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

Vol. 15 | Weekly issue 41 | 14 October 2010

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

First autochthonous malaria case due to *Plasmodium vivax* since eradication, Spain, October 2010

P Santa-Olalla Peralta (psantaolalla@msps.es)[1], M C Vazquez-Torres[1], E Latorre-Fandós[2], P Mairal-Claver[3], P Cortina-Solano[4], A Puy-Azón[4], B Adiego Sancho[5], K Leitmeyer[6], J Lucientes-Curdi[7], M J Sierra-Moros[1]

1. Coordinating Centre for Health Alerts and Emergencies, Ministry of Health and Social Policy, Madrid, Spain
2. Haematology Department, Hospital San Jorge, Huesca, Spain
3. Microbiology Department, Hospital San Jorge, Huesca, Spain
4. Sub-directorate General of Public Health of Huesca, Regional Health Service of Aragón, Huesca, Spain
5. Service of Public Health Surveillance, Directorate General of Public Health of Aragón, Regional Health Service of Aragón, Zaragoza, Spain
6. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
7. Animal Pathology Department, Veterinary School, Universidad de Zaragoza, Zaragoza, Spain

Citation style for this article:
Santa-Olalla Peralta P, Vazquez-Torres MC, Latorre-Fandós E, Mairal-Claver P, Cortina-Solano P, Puy-Azón A, Adiego Sancho B, Leitmeyer K, Lucientes-Curdi J, Sierra-Moros MJ. First autochthonous malaria case due to Plasmodium vivax since eradication, Spain, October 2010. Euro Surveill. 2010;15(41):pii=19684. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19684

Article published on 14 October 2010

In October 2010, one case of autochthonous malaria due to *Plasmodium vivax* was diagnosed in Spain. The case occurred in Aragon, north-eastern Spain, where the vector *Anopheles atroparvus* is present. Although the source of infection could not be identified, this event highlights that sporadic autochthonous transmission of vector-borne diseases in continental Europe is possible and calls for enhanced surveillance and vector control measures.

Background

Malaria is a mosquito-borne parasitaemic disease caused by parasites of the *Plasmodium* genus and endemic in Africa, Asia, Central and South America. According to the World Health Organization (WHO), there were 247 million cases of malaria and nearly one million deaths worldwide in 2008, mostly among children living in Africa [1]. Four species of *Plasmodium* have long been recognised to infect humans in nature: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Recently, the simian parasite *P. knowlesi* has been found as a cause of human malaria in some areas of south-east Asia [2]. Worldwide, *P. falciparum* and *P. vivax* are the most common causes of malaria. The malaria parasites are transmitted by female *Anopheles* mosquito vectors. Of the approximately 430 *Anopheles* species, only 20 species are important for transmission.

Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death in the case of *P. falciparum* malaria. The main symptoms of malaria include episodes of cyclical or irregular fever, chills, headache, weakness, vomiting and diarrhoea. The incubation period in most cases varies from seven to thirty days after the infective mosquito bite.

In *P. vivax* malaria, the incubation period usually ranges from 10 to 21 days and sometimes up to a year. Unlike *P. falciparum* malaria, *P. vivax* malaria is rarely fatal. However, for *P. vivax*, clinical relapses may occur weeks to months after the first infection. These new episodes arise from dormant forms in the liver, and special treatment with primaquine – targeted at these liver stages – is mandatory for a complete cure.

Situation in Europe and Spain

Within the WHO European Region, six countries reported autochthonous malaria infections in 2008 caused by *P. vivax*: Azerbaijan, Georgia, Kyrgyzstan, Tajikistan (the only country in the Region reporting *P. falciparum* malaria), Turkey and Uzbekistan [3]. In the European Union (EU) and European Economic Area (EEA) countries, malaria has been eradicated since 1975 and nearly all reported malaria cases are imported. In 2008, 5,848 malaria cases were reported; the vast majority of cases for which the species was known were caused by *P. falciparum* (78%) while less than 10% were caused by *P. vivax* [4]. During the last 10 years, less than 20 cases of autochthonous transmission of malaria have been reported in the EU/EEA [3,5]. Despite the presence of potential anopheline vectors in some countries, sustained local transmission has not been identified in continental EU countries [5].

In Spain, the last autochthonous case of malaria was reported in 1961 [6] and malaria was officially declared eradicated in 1964. According to the Spanish National Surveillance Network, an average of 400 imported malaria cases are reported each year (with less than 5% due to *P. vivax*). The Spanish population is susceptible to malaria infection given the absence or disappearance of the immunity acquired in the past by contact with the parasite.

The principal potential anopheline vector of malaria in Spain is *Anopheles atroparvus* which is widely distributed throughout Spain (Figure) and can transmit Asiatic strains of *P. vivax* but is refractory to African strains of *P. falciparum* [7].

Case report

On 5 October 2010, the Regional Health Authorities of Aragon reported to the Coordinating Centre for Health Alerts and Emergencies at the Spanish Ministry of Health one laboratory-confirmed case of *P. vivax* malaria in a patient in their 40s living in the province of Huesca (Region of Aragon). The patient had developed fever on 20 September 2010 and was diagnosed on 25 September with acute tonsillitis and started treatment with amoxicillin and ibuprofen. Four days later, the patient was hospitalised because of clinical deterioration with fever and jaundice. On the same day, *Plasmodium* spp. parasites were detected in the blood smear, and antimalarial treatment with chloroquine and primaquine was initiated. On 1 October the patient was dismissed in good clinical condition.

Laboratory results

Detection of macrocytosis on the first blood sample taken upon hospital admission led to a Giemsa staining where *Plasmodium* spp. parasites were unexpectedly identified. Further tests (Rapid Test Binax, chromatography) diagnosed *Plasmodium* spp. (non-*falciparum*). On 4 October, the National Centre for Microbiology in Madrid (National Reference Laboratory) confirmed the presence of *P. vivax* by microscopy and multiplex PCR. Genomic analysis of the parasite is still ongoing.

Epidemiological investigation

According to the epidemiological investigation, the patient did not have any travel history to an endemic/epidemic area ever, or contact to persons visiting or residing in such areas. There was no history of surgeries, invasive examinations or diagnostics, or blood transfusions. The patient never was an injecting drug user or had any treatments involving injections. The patient reported two visits to airports, Barcelona airport in summer 2008 and Zaragoza airport in summer 2009.

In the vicinity of the patient's residence there were swine exploitations and was frequently exposed to mosquito bites. Furthermore, the patient lives in an area of the province of Huesca where *An. atroparvus* is present in several nearby localities. No malaria cases have been reported amongst the case's contacts or residents in the locality. There have been no reports of imported malaria cases from this area in recent years, including 2010.

Figure

Distribution of *Anopheles atroparvus* in Spain (dots indicate presence)

Control measures

The implemented control measures included testing household members for malaria, active case finding in the neighbourhood of the case and through alerting healthcare centres (including hospitals) in the area, as well as entomological survey and vector control. The entomological survey carried out so far has not proven the presence of *Plasmodium* parasites in local mosquitoes.

Risk assessment for Spain

Although the investigation was very detailed, we have not been able to identify the source of infection. Ongoing genetic analysis of the parasite may help to specify its possible origin. Transmission may have occurred through local *Anopheles* species after infection from people coming from endemic areas carrying gametocytes in their blood. Airport malaria caused by infected mosquitoes imported from endemic areas seems improbable due to the distance to the next international airport (approx. 100 km) and the limited flight range of local anophelines (4.5 km).

The possibility of a secondary case originating from the reported case is unlikely as the patient has been treated, comprehensive control measures have been implemented, and the person had never donated blood.

In Spain, the situation following the eradication of malaria in 1964 is defined as 'anophelism without malaria' with the presence of potential vectors for the parasite (mainly *An. atroparvus*, which is a species refractory to *P. falciparum*) and environmental conditions favourable for the breeding, development and permanence of the vector [7]. The risk for local transmission of malaria will depend on the presence of parasitaemic individuals and competent vectors at a given time and place. This risk is reduced by early and appropriate detection and treatment of cases and vector control activities in place. However, it is still possible that other sporadic autochthonous cases could still be identified.

Conclusions

Given the described conditions in Spain, an autochthonous case of malaria is not unexpected. Previous events, including the occurrence of several emerging vector-borne disease outbreaks in different countries in Europe, indicate that sporadic autochthonous transmission of vector-borne diseases in continental Europe is possible [9-11].

The available epidemiological information does not suggest that there is a risk for human health in the area. The epidemiological investigation suggested that this was a sporadic case with no evidence of further local transmission. With the current information, this event does not pose a significant risk to EU/EEA citizens. Despite the fact that autochthonous cases have been reported sporadically in the EU in the past, such cases never resulted in established local transmission involving more than a few cases.

Given the presence of competent vectors for malaria in the EU, we cannot exclude similar events in the future. Continued monitoring of the situation in areas where *Anopheles* mosquito populations are present is needed, including increased awareness among clinicians, to rapidly identify and report suspected malaria cases to respective authorities, and ensure an appropriate public health response.

References

1. World Health Organisation (WHO). Fact sheet No 94. April 2010. Malaria. Geneva: World Health Organization; 2010. Available from: http://www.who.int/mediacentre/factsheets/fs094/en/index.html.
2. Luchavez J, Espino F, Curameng P, Espina R, Bell D, Chiodini P, et al. Human Infections with Plasmodium knowlesi, the Philippines. Emerg Infect Dis. 2008 May;14(5):811-3.
3. World Health Organisation (WHO), Regional Office for Europe. [Internet]. Centralized information system for infectious diseases (CISID) database. Malaria. Copenhagen: World Health Organization; 2010. Available from: http://data.euro.who.int/cisid/
4. European Centre for Disease Prevention and Control (ECDC). The European Surveillance System (TESSy). TESSy database. Data source 2008. Stockholm: World Health Organisation; 2010.
5. Alten B, Kampen CH, Fontenille D, eds. Malaria in Southern Europe: resurgence from the past? Emerging Pests and Vector-Borne Diseases in Europe, ed. W. Takken and B. Knols. 2007, Wageningen Academic Publishers, Wageningen, The Netherlands. 35-58.
6. Clavero G. [The eradication of malaria in Spain]. Rev San Hig Publ. 1961. 35: p. 265-92. Spanish.
7. Bueno Marí R, Jiménez Peydró R. [Malaria in Spain: entomological aspects and future outlook]. Rev Esp Salud Pública. 2008;82(5):467-79. Spanish.
8. Delacour S, Melero-Alcibar R, Aranda C, Cortés M, Eritja R, Escosa R et al. Detailed maps of the geographical distribution of the mosquitoes of Spain based on a literature review. Part II: Genus Anopheles. The 5th European Mosquito Control Association Workshop. Turin Italy (2009).
9. Schmidt-Chanasit J, Haditsch M, Schöneberg I, Günther S, Stark K, Frank C. Dengue virus infection in a traveller returning from Croatia to Germany. Euro Surveill. 2010;15(40):pii=19677. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19677
10. La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P, et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010;15(39):pii=19676. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19676
11. Institut de Veille Sanitaire (InVS, French Institute for Public Health Surveillance). [Autochtnous cases of chikungunya infection in the Var] 27 September 2010. Available from: http://www.invs.sante.fr/regions/sud/pe_paca_corse_011010.pdf

Travel-associated Legionnaires' disease in Europe in 2009

C A Joseph (cajoseph75@hotmail.com)[1], K D Ricketts[1], R Yadav[1], S Patel[1], on behalf of the European Working Group for Legionella Infections
1. Centre for Infections, Health Protection Agency, London, United Kingdom

Citation style for this article:
Joseph CA, Ricketts KD, Yadav R, Patel S, on behalf of the European Working Group for Legionella Infections. Travel-associated Legionnaires' disease in Europe in 2009. Euro Surveill. 2010;15(41):pii=19683. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19683

Article published on 14 October 2010

A total of 818 cases of Legionnaires' disease with onset of illness in 2009 were reported from 22 European and two non-European countries to the European Surveillance Scheme for Travel-Associated Legionnaires' Disease (EWGLINET). This is a decrease of 52 cases compared with 2008 and 129 fewer than in 2007 - the peak year of reporting to date. A total of 794 (97.1%) cases were reported as confirmed and 24 as presumptive cases. Outcome of illness was reported for 561 (68.6%) cases. Of these cases 28 (5%) were reported to have died. More than half, of the cases in 2009 (n=469, 57.3%) were reported within 20 days of symptom onset. Cases visited 53 countries and were infected in all months of the year, with a peak in September (n=146). By country of residence of the cases, the United Kingdom (UK) reported the highest number of cases (n=173). Italy reported the second highest number of cases (n=169) and was also the country associated with the most cases by country of infection (n=209). A total of 88 new clusters (75 in Europe and 13 outside Europe) were detected in 2009 and were associated with 196 cases. The largest cluster occurred in Italy and involved seven cases. Without the scheme's international database, thirty three (37.5%) of the newly detected clusters would not have been identified. In 49 of the accommodation sites with clusters of cases, environmental samples were found to be positive for *Legionella* spp. Details of 10 sites were published on the European Working Group for Legionella Infections (EWGLI) website for failure to return information on the status of environmental investigations.

Introduction

The European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) was established in 1987 by the European Working Group for Legionella Infections (EWGLI), one year after EWGLI itself was formed. From 1993 to March 2010 the scheme was run as a European Union (EU) funded disease specific network through a coordinating centre in London, United Kingdom (UK), with the common aim among collaborating countries of detection, response, control and prevention of cases and clusters of Legionnaires' disease specifically associated with public accommodation sites used by travellers.

European guidelines for the control and prevention of travel-associated Legionnaires' disease were introduced by EWGLI in 2002, and endorsed by the European Commission in 2003 [1]. They were produced to ensure consistency of approach and a common high standard for investigation of cases and clusters in order to improve protection for travellers throughout Europe.

In April 2010 the scheme was transferred to the European Centre for Disease Prevention and Control (ECDC) and renamed ELDSNet, retaining the original aims and objectives of the network [2]. This paper documents and comments on cases of travel-associated Legionnaires' disease reported to EWGLINET with an onset of illness in 2009.

Methods

Legionnaires' disease is normally diagnosed in the country of residence of the case and reported from the local or regional level to the country's own national surveillance scheme. Cases that met the microbiological case definitions of the European surveillance scheme [2] were defined as travel-associated if they stayed overnight in a hotel or other type of public accommodation site for at least one night in the two to 10 days before onset of their illness. A secure part of the EWGLI website was used by collaborating countries to electronically report these cases to the international database held by the coordinating centre at the Health Protection Agency (HPA) Centre for Infections in London. Information on the epidemiology, microbiology and travel history of each new case was provided. The database was then searched to determine whether each new case should be classified as a single case or part of a cluster, using the definitions below:

- A single case: a person who stayed at a public accommodation site in the two to 10 days before onset of illness and the site was not associated with any other case of Legionnaires' disease in the previous two years.
- A cluster: two or more cases who stayed at the same public accommodation site in the two to 10 days before onset of illness and whose onsets were within the same two year period.

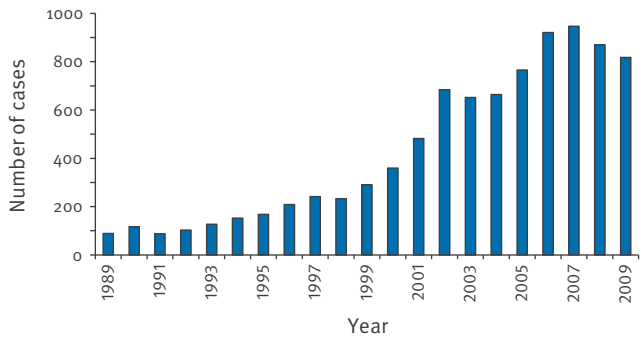
These definitions determine the response that is expected by the country where the case became infected within the EU and other EWGLINET (now ELDSNet) countries that have signed up to using EWGLI's guidelines [1]. For single cases, infection could have been acquired from any number of potential sources in the two to 10 days before onset of illness, the accommodation site being just one of them. The guidelines require that the collaborator in the country of infection is informed of the case. He or she must then send the 14 point checklist to the case's accommodation site in order for the site's managers to ensure they are following best practice and one that minimises any potential risk of legionella infection for its guests [1]. This is the only action required at the international level but some countries in the scheme choose to investigate further in accordance with their own national protocols.

Clusters sometimes involve single cases from two or more countries and as such would not normally be recognised as being linked to a specific accommodation site through national surveillance systems alone. It is now the role of the ELDSNet coordinating centre to identify these clusters and ensure they are included in the actions required of all clusters as described below.

When a cluster is detected, all collaborators in the scheme are informed of the incident. A full investigation is required in the country of infection and preliminary results from the risk assessment and start of control measures should be reported back to the coordinating centre within two weeks of the alert, using the guidelines' Form A. A Form B is then used to report the results of environmental sampling and the control measures applied to the site, back to the coordinating centre within a further four weeks, thus allowing six weeks in total for all investigations to be completed. If the forms are not returned within the specified time frames, or they report that actions and control measures are unsatisfactory, ELDSNet publishes the details of the sites associated with the cluster on its website.

Figure 1

Number of travel-associated cases of Legionnaires' disease reported to EWGLINET, 1989-2009 (n=8,995)



EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease

By putting the information in the public domain, individual travellers and tour operators alike can decide for themselves whether or not they wish to contract with these sites. Information is removed from the website when the investigations are reported to have been satisfactorily completed.

Additional cases of Legionnaires' disease are sometimes associated with sites where investigations were reported to have been completed satisfactorily. If these occur within two years of the original cluster, the site becomes a 'reoffender' and a new investigation is required. If a cluster is associated with more than one accommodation site, it is noted as a 'complex cluster' and all sites stayed at by the cluster cases are subject to the investigation procedures as laid down in the guidelines.

Each spring, countries that participate in the scheme are requested to submit their annual dataset of all cases of Legionnaires' disease in residents of their country with onset of illness in the preceding year, together with population data by age group for calculating incidence rates by standardised age groups. Aggregated population data from the countries that reported cases of travel-associated Legionnaires' disease in 2009 was used to calculate incidence rates by standardised age groups for these cases.

Results

A total of 818 cases of travel associated Legionnaires' disease with onset of infection in 2009 were reported to EWGLINET. This number is 52 cases fewer than the 870 cases reported in 2008 and 129 fewer than when the peak of 947 cases was reported in 2007 (Figure 1). Cases were reported from 22 EWGLINET collaborating countries (United Kingdom (UK) counted as three separate countries) and two countries outside the scheme

Table 1

Countries reporting more than 10 cases of travel-associated Legionnaires' disease to EWGLINET in 2008–2009[a]

Country of report	Number of cases	
	2008	2009
United Kingdom	166	173
Italy	127	169
France	191	163
The Netherlands	127	109
Spain	97	65
Denmark	38	34
Sweden	35	22
Norway	21	17
Austria	20	17
Belgium	11	12

EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease

[a] A further 14 countries (including the US and New Zealand) reported fewer than 10 cases, and are not listed here.

(United States (US) and New Zealand). The countries that reported the most cases were the UK (n=173), Italy (n=169), France (n=163), and the Netherlands (n=109) (Table 1). These four countries have consistently reported the highest number of cases to the scheme over several years [3,4].

The mean interval between onset of illness and report to the scheme in 2009 was 29 days (range 2 - 415 days, median 17 days), compared with 27 days in 2008 (range 1-300 days, median 15 days). 176 (21.5%) cases were reported within 10 days of onset, 469 (57.3%) within 20 days and 606 (74.1%) within 30 days. The excessive delay in reporting of some cases was due to delays in obtaining and transmitting the required case information from the country's local or regional office to the national collaborating centre and onwards to the EWGLINET scheme.

The male to female ratio in 2009 was 2.7:1 where 597 (73%) cases were male and 221 (27%) were female. Cases were reported in all age groups (range 19-92 years for males (median 60 years) and 17-88 years (median 64 years) for females). For males the highest number of cases (167) was in the 50-59 year age group whereas for women it was in the 60-69 years age group at 79 cases. Using 2008 population statistics provided by individual EWGLINET countries from their annual return of their national dataset of all cases of Legionnaires' disease, the aggregated age-standardised incidence rates for the 22 European countries that reported cases show that rates per 100,000 population by age group increased with increasing age for males and females combined up to age 60-69 years and then decreased again for the 70-79 year-olds and in those aged 80 years or older (Figure 2).

Outcome of illness was reported for 561 (68.6%) cases. Of these cases 28 (5%) were reported to have died, a far lower proportion than the 9.8% in 2008. Of those that died in 2009, 20 were males, 17 of whom were between 50 and 79 years of age and eight were females aged between 40 and 89 years. A total of 310 cases (55.25%) recovered, and 223 cases (39.75%) were still ill at time of report. For the remaining 257 cases the outcome was unknown.

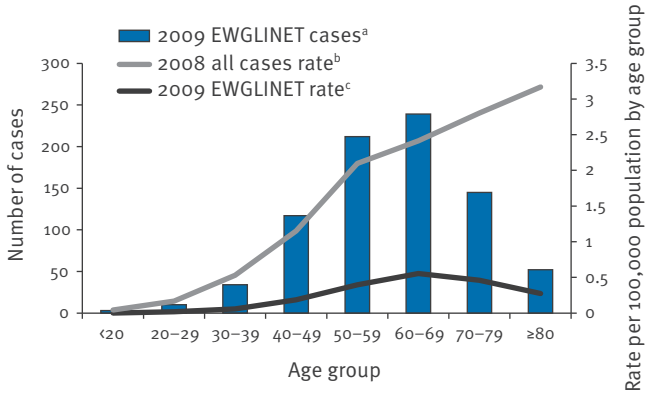
The number of cases with Legionnaires' disease normally increases in warmer weather and this travel-associated surveillance scheme highlights this observation. Cases peaked in September (n=146) but occurred in all months of the year (range 20 – 146 per month).

Microbiological analysis

On the basis of the EWGLINET case definition, 794 (97.1%) cases were reported as confirmed cases in 2009. Of these, 82 (10%) were diagnosed by culture of the organism, an increase from 7.7% in 2008 and 8.2% in 2007. Of the culture-confirmed cases, 54 were also diagnosed by urinary antigen detection and a further 701 (85.7%) cases were diagnosed by detection of urinary antigen alone. A total of 11 cases (1.3%) were confirmed by a four-fold rise in antibody response to *L. pneumophila* serogroup 1 infection. The remaining 24 (2.9%) cases were presumptively diagnosed, 15 (1.8%) by single high titre and nine (1.1%) by PCR. Altogether, 712 (87%) cases were reported as *L. pneumophila* serogroup 1, 13 (1.6%) as *L. pneumophila* other serogroup, 73 (8.9%) as *L. pneumophila* serogroup unknown, one as *Legionella* other species (*L. micdadei* or *L. bozemanii*) and 19 (2.3%) as *Legionella* species unknown. Of the *L. pneumophila* other serogroups (sgs), two were sg2, two were sg3, two were sg5, one was sg8, one

Figure 2

Age group and age-standardised incidence rates for cases of travel-associated Legionnaires' disease reported to EWGLINET in 2009 compared with age-standardised incidence rates obtained from the total European dataset of 2008



EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease

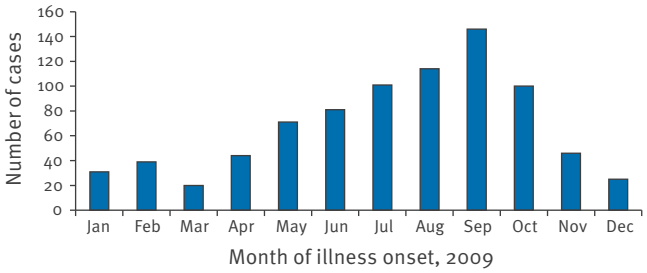
[a] Number of 2009 EWGLINET cases by age group.

[b] The 2008 age specific incidence rate is calculated from population data by age group for EWGLINET countries that submitted an annual return of their national dataset to the EWGLINET coordinating centre [6].

[c] The 2009 age specific incidence rates for travel-associated cases was calculated from the 2008 aggregated population data using only those countries that reported cases of travel-associated Legionnaires' disease in 2009.

Figure 3

Month of illness onset for cases with Legionnaires' disease reported to EWGLINET, 2009 (n=818)



EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease

was sg1-7, one was sg10 and four were sg unknown. PCR was used in conjunction with culture for 22 cases, 18 of which were reported by Denmark, and as a single method of diagnosis for nine cases, seven of which were reported by the Netherlands.

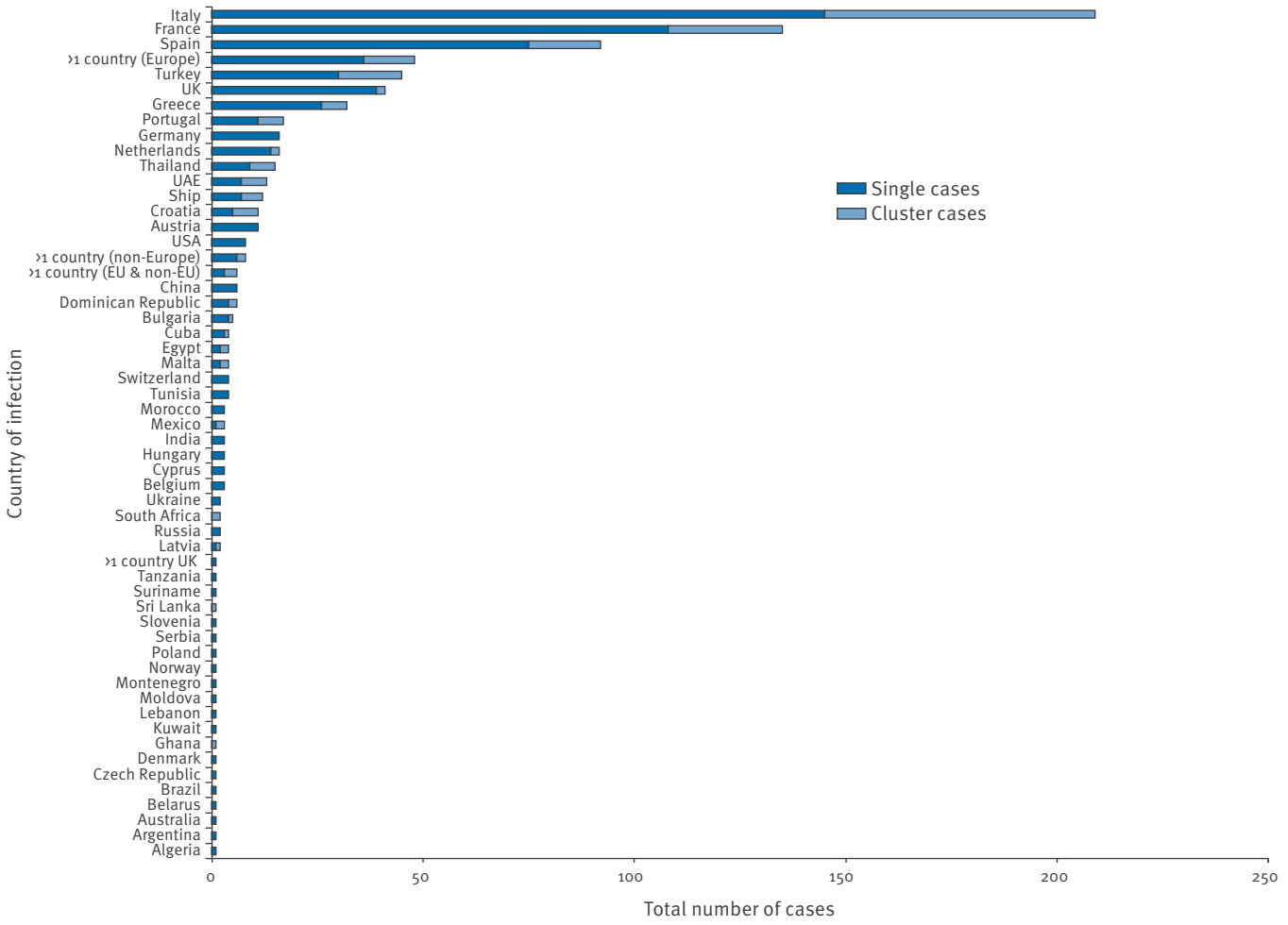
Travel

Cases visited a total of 53 countries in the 2-10 days before onset of legionella infection. 655 (80%) cases went to one country only (giving a total of 26 countries visited) in Europe, and 49 (6%) to more than one European country. Ninety six (11.7%) cases travelled outside Europe, 88 (10.8%) to single destinations in 27 countries and eight (1%) to more than one non-European country. Six cases (0.7%) went to both European and non-European destinations and 12 (1.5%) cases were associated with cruise ships. Italy was the country associated with the most cases (n=209) followed by France (135 cases), Spain (92 cases) and Turkey (45 cases).

Different travel patterns emerge when country of report and country of travel are analysed together. The data show that most northern Europeans travel south and become infected abroad whereas many southern European residents have the country of residence and country of infection in common. For instance, France reported that 99 of 135 cases (73%) who acquired Legionnaires' disease as a result of travel in France were linked to internal travel by French nationals and 20% of the cases that travelled in France were associated with clusters (down from 23.2% in 2008). Of the 209 cases who acquired Legionnaires' disease in Italy, 125 (60%) were related to internal travel by Italian nationals and 64 (30.6%) were associated with clusters (down from 39% in 2008). Among northern European residents the majority of cases acquired their infection as a result of travel abroad and few cases are associated with their home countries. However, of the 42 cases acquired in the UK, 38 were UK nationals and in the Netherlands 15 of 16 cases acquired in this country were Dutch nationals. The data also show that certain nationals have a preference for travel to particular

Figure 4

Countries visited by cases with travel-associated Legionnaires' disease in 2009, by type of case, EWGLINET data



EU: European Union; EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease; UAE: United Arab Emirates; UK: United Kingdom; US: United States.

countries. For example 16 (14.7%) of Dutch cases compared with 16 (9.3%) of UK cases were linked to travel in Turkey whereas for travel to Spain, the proportion was much higher among UK cases at 31 (18%) compared with only 6 (5.5%) for Dutch cases.

Clusters

A total of 88 new clusters (75 in Europe and 13 outside Europe) were detected in 2009 and were associated with 196 (24%) cases of Legionnaires' disease, five of whom died. Seven cases were associated with the largest cluster in 2009 which occurred in Italy. This country was associated with the highest number of clusters (26) followed by France (16), Turkey (10) and Spain (9). Altogether clusters in Europe occurred in 14 different countries and on two cruise ships. Outside Europe the 13 clusters occurred in nine countries and on one cruise ship. A total of 33 clusters (37.5%) comprised a single case reported from two or more countries and would not have been detected without the scheme's international database. Clusters were detected in every month of the year but were more common in the months between June and October when 47 (53.4%) were detected and again in December when nine occurred.

Investigations and publication

Some of the clusters involved more than one site (complex clusters). In total, 97 sites were linked to the 88 new clusters detected in 2009. Of these sites, 15 were located outside Europe in countries that were not signed up to follow the European guidelines, leaving 82 sites that required EWGLINET investigations. Cluster updates were also issued for 32 'reoffending sites' in 2009 (compared with 35 in 2008). Of the reoffending sites, 20 were situated in Italy, one in France, two in Spain, three in Turkey, two in Greece, and one each in Latvia, Malta, Portugal and Switzerland.

Thus 114 sites in Europe (82 original sites and 32 reoffending sites) required investigation in 2009 according to the procedures outlined in the European guidelines. From these investigations, collaborators reported that *Legionella* spp. was detected in water samples from 32 of the 82 EWGLINET cluster sites and 17 of the 32 reoffending sites. Thus overall 49 (43%) sites were positive for *Legionella* spp., a similar proportion to 2008 when 42.1% of EWGLINET sites were reported as positive for *Legionella* spp. No *Legionella* spp. were detected from 56 (49.1%) investigation sites, six sites were closed and therefore could not be investigated, results were still awaited at two sites and one site had not returned results on the forms A and B within the six-week period specified by the European guidelines.

Although not required to do so, the results of environmental investigations were reported to EWGLINET for eight cluster sites outside Europe. Four of these were in Thailand where three tested positive for *L. pneumophila* sg1. One site with positive results was reported from a cluster in each of South Africa, the United Arab Emirates and the US. A negative result was reported from a cruise ship cluster investigated in the Middle East.

A total of 10 accommodation sites were published on the EWGLI website in 2009, either due to failure to submit a Form A or B within the specified time period of the European guidelines or because it was reported that the appropriate control measures were not in place. Publishing an accommodation site on the EWGLI website is a means of alerting professionals and the public to the fact that investigation results are unknown or that the control measures have been reported as unsatisfactory. Four of these sites were located in Turkey, three in Italy and one each in Bulgaria, France and Portugal.

Table 2

Countries where two or more clusters of travel-associated Legionnaires' disease occurred in 2009, EWGLINET data[a]

Country of infection	Number of clusters
Europe	
Italy	26
France	16
Turkey	10
Spain	9
Portugal	3
Greece	2
Not specified[b]	2
Non-Europe	
Cuba	2
South Africa	2
Thailand	2

EWGLINET: European Surveillance Scheme for Travel-Associated Legionnaires' Disease

[a] A further thirteen countries and one cruise ship were associated with only one cluster and are not listed here.

[b] Ship

Discussion

Compared with 2008 and 2007, 2009 was associated with a further decrease in travel-associated Legionnaires' disease. This fall may continue to reflect a decrease in the global number of travellers and the impact of the world-wide recession on travel and tourism. More than 922 million travel arrivals worldwide were estimated in 2008 compared with 880 million in 2009 [5]. However, there is also some evidence that improved control and prevention of infection in hotels and other public accommodation sites may be contributing to this decline, particularly where clusters are concerned. The number of detected clusters has fallen from 92 in Europe in 2008 to 75 in 2009 and the overall proportion of cases associated with clusters was at its lowest in 2009 at 24% compared with 29.1% in 2008 and 32% in 2007. Falls in the number of both single and cluster cases are especially evident in countries that traditionally have a high number of cases such as

France and Spain. Although Italy was associated with an increase in cases in 2009 compared with 2008, the proportion of cluster cases there was also down from the year before from 39% to 31.6%. A far lower proportion of deaths (5%) were recorded in 2009 from the 561 cases (68.6%) with a known outcome compared with the 9.8% of known deaths in 2008.

When all cases of Legionnaires' disease are analysed together at the national level, most countries see that the incidence of disease rises by increasing age group when age-standardised rates are calculated [6]. For travel-associated cases age-standardised rates did not show a rise in incidence with increasing age after the age of 69 years, although almost one quarter of the reported cases in both 2008 and 2009 were aged 70 years or more. It is unlikely that under-diagnosis of *Legionella* spp. infections linked to travel account for the difference in incidence rates for this subset of national cases. Instead it is more likely that relative opportunities for exposure between travel cases and community-acquired cases are different, with only a small proportion of elderly persons travelling from this population age group. However, if the absolute number of travellers among the elderly increases in future years and a higher proportion of cases will occur in this age group, there may well be an associated increase in incidence based on age-standardised rates.

The overall proportion of cluster sites positive for *Legionella* spp. has remained similar for the last two years at 43% and 42% respectively, although positivity rates were higher for the reoffending sites in 2009 compared with 2008. It could be that a plateau has been reached in the level of positive investigation results for new clusters. This may be related to better awareness of control and prevention procedures at these sites and an increased acknowledgement that some clusters occur by chance and that exposure to infection may have occurred elsewhere. With fewer clusters occurring each year, and a smaller proportion of cluster cases in the total dataset, perhaps more attention should now be given to investigating accommodation sites associated with new single cases. These sites would not have been subject to any previous contact with EWGLINET, nor received its advice on minimising risk from *Legionella* spp. in water systems.

The management of clusters associated with cruise ships is often problematic for EWGLINET as by nature they are more difficult to deal with than clusters in hotels. The ship's sailing itinerary at the time of cluster notification (rather than cluster occurrence) must be established in order to determine through which European country it is appropriate to request investigations. If the ship's itinerary is outside Europe, investigations will be requested through a relevant national public health institute, the World Health Organization (WHO), or via the tour operator or health and safety department of the cruise company. However, opportunities to board the ship and carry out a risk assessment and sampling are usually very limited as the length of time spent in port can be as short as a few hours. EWGLINET has no powers to restrict a ship in port while investigations proceed.

The number of accommodation sites published on the EWGLI website in 2009 fell again compared with 2008 and 2007. Turkey still has a high proportion of its clusters (40% in 2009, 50% in 2008) appearing on the website for failure to complete investigations on time, but in absolute terms it no longer stands out as a country experiencing problems in meeting the follow-up requirements as specified in the EWGLI guidelines.

It is encouraging to note that more information on clusters occurring outside Europe has been fed back to EWGLINET. Thailand used the EWGLI guidelines to manage their two clusters in 2009 and completed forms A and B, as did health and safety officials involved with the Middle East cruise ship cluster, and the clusters in the United Arab Emirates and South Africa. In the US, the Centers for Disease Control and Prevention also returned information to EWGLINET on their cluster investigations. This feedback has evolved through improved contacts with collaborators in these countries although assistance from WHO is still required to raise awareness of EWGLINET standards elsewhere.
This is the final report of the EWGLINET surveillance scheme in this series; the first report appeared in 1996 [7]. ECDC is now responsible for the scheme, which was renamed ELDSNet in April 2010. The authors hope that ECDC will continue to publish this important data on a regular basis in the future.

Acknowledgements

This work was funded by the ECDC. We would like to thank all the collaborators for reporting their cases and all persons involved in public health programmes for the control and prevention of travel associated Legionnaires' disease. A list of current collaborating centres can be found on the ECDC website [8].

References

1. European Working Group for Legionella Infections. European Guidelines for Control and Prevention of Travel Associated Legionnaires' Disease. Available from: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/LegionnairesDisease/Guidlines/legiEuropeanAdviceandGuidance/
2. European Centre for Disease Prevention and Control (ECDC). Stockholm: EWGLINET case definition. Available from: http://ecdc.europa.eu/en/activities/surveillance/ELDSNet/Pages/EU%20case%20definition.aspx
3. Ricketts K, Joseph CA, Yadav R, on behalf of the European Working Group for Legionella Infections. Travel-associated Legionnaires' disease in Europe in 2008. Euro Surveill. 2010;15(21):pii=19578. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19578
4. Joseph CA, Yadav R, Ricketts KD, on behalf of the European Working Group for Legionella Infections. Travel-associated Legionnaires' disease in Europe in 2007. Euro Surveill. 2009;14(18):pii=19196. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19196
5. World Tourism Organization (UNWTO). World Tourism Barometer January 2010. Madrid; 2010. Available from: http://www.unwto.org/facts/eng/pdf/barometer/UNWTO_Barom10_1_en_excerpt.pdf.

6. Joseph CA, Ricketts KD, on behalf of the European Working Group for Legionella Infections. Legionnaires' disease in Europe 2007–2008. Euro Surveill. 2010;15(8):pii=19493. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19493
7. Hutchinson EJ, Joseph C, Bartlett CL. EWGLI: a European surveillance scheme for travel associated legionnaire's disease. Euro Surveill. 1996;1(5):pii=169. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=169
8. European Centre for Disease Prevention and Control (ECDC). [Internet]. Stockholm: ELDSNet. Participating institutions. Available from: http://www.ecdc.europa.eu/en/activities/surveillance/ELDSNet/Pages/Participating_institutions.aspx

Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe

R Köck[1,2], K Becker[2], B Cookson[3], J E van Gemert-Pijnen[4], S Harbarth[5,6], J Kluytmans[7,8], M Mielke[9], G Peters[2], R L Skov[10], M J Struelens[11,12], E Tacconelli[13], A Navarro Torné[12], W Witte[14], A W Friedrich (alexander.friedrich@ukmuenster.de)[1]

1. Institute of Hygiene, University Hospital Muenster, Muenster, Germany
2. Institute of Medical Microbiology, University Hospital Muenster, Muenster, Germany
3. Laboratory of Healthcare Associated Infections, Centre for Infections, Health Protection Agency, London, United Kingdom
4. Faculty of Behavioural Sciences, University of Twente, Enschede, the Netherlands
5. Infection Control Program, University Hospitals of Geneva, Geneva, Switzerland
6. University of Geneva Medical School, Geneva, Switzerland
7. VU University Medical Centre, Amsterdam
8. Amphia Hospital, Breda, the Netherlands
9. Robert Koch Institute, Berlin, Germany
10. Statens Serum Institut (SSI, National Centre for Infectious Diseases), Copenhagen, Denmark
11. Department of Microbiology, Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium (affiliation where the work was started)
12. Scientific Advice Unit, European Centre for Disease Prevention and Control, Stockholm, Sweden
13. Department of Infectious Diseases, Università Cattolica Sacro Cuore, Rome, Italy
14. National Reference Centre for Staphylococci, Robert Koch Institute, Wernigerode, Germany

Citation style for this article:
Köck R, Becker K, Cookson B, van Gemert-Pijnen JE, Harbarth S, Kluytmans J, Mielke M, Peters G, Skov RL, Struelens MJ, Tacconelli E, Navarro Torné A, Witte W, Friedrich AW. Methicillin-resistant Staphylococcus aureus (MRSA): burden of disease and control challenges in Europe. Euro Surveill. 2010;15(41):pii=19688. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19688

Article published on 14 October 2010

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare- and community-associated infections worldwide. Within the healthcare setting alone, MRSA infections are estimated to affect more than 150,000 patients annually in the European Union (EU), resulting in attributable extra in-hospital costs of EUR 380 million for EU healthcare systems. Pan-European surveillance data on bloodstream infections show marked variability among EU Member States in the proportion of *S. aureus* that are methicillin-resistant, ranging from less than 1% to more than 50%. In the past five years, the MRSA bacteraemia rates have decreased significantly in 10 EU countries with higher endemic rates of MRSA infections. In addition to healthcare-associated infections, new MRSA strains have recently emerged as community- and livestock-associated human pathogens in most EU Member States. The prevention and control of MRSA have therefore been identified as public health priorities in the EU. In this review, we describe the current burden of MRSA infections in healthcare and community settings across Europe and outline the main threats caused by recent changes in the epidemiology of MRSA. Thereby, we aim at identifying unmet needs of surveillance, prevention and control of MRSA in Europe.

Introduction

Concern about the burden of healthcare-associated infections (HAIs) has a significant European dimension. It has been estimated that 8–12% of patients admitted to hospitals in European countries suffer from adverse events while receiving healthcare, with HAIs being the most prominent of them [1]. The European Centre for Disease Prevention and Control (ECDC) has calculated that HAIs involve 4.1 million patients annually in the European Union (EU) Member States and that such infections directly result in approximately 37,000 deaths [1]. This worrisome incidence of HAIs is rightly considered a major patient safety issue. Another cause for concern is the continuous emergence of various multidrug-resistant bacteria in many healthcare institutions, which narrows the spectrum of effective antibiotics to a clinically challenging extent. Against this background, the Council of the EU has recently launched a recommendation to Member States and the Commission to prevent HAIs and promote patient safety by community, national and institutional action plans [1].

Among the multiresistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of HAIs in the EU. In 2008, over 380,000 HAIs due to selected antibiotic-resistant bacteria, including those of the bloodstream, lower respiratory tract, skin or soft tissues and urinary tract, were estimated to be acquired annually in hospitals of the EU Member States, Iceland and Norway [2]. Overall, MRSA accounts for 44% (n=171,200) of these HAIs, 22% (n=5,400) of attributable extra deaths and 41% (n=1,050,000) of extra days of hospitalisation associated with these infections [2]. The attributable extra in-hospital costs caused by MRSA are estimated to reach approximately EUR 380 million annually [2]. Moreover, the vast extent of MRSA infections has both evoked fear and fuelled public distrust about healthcare. For many healthcare

consumers, this has made MRSA bloodstream infection rates an indicator of both quality of care and outcome.

In addition to the healthcare settings (healthcare-associated methicillin-resistant *Staphylococcus aureus*, HA-MRSA) [3], the burden of MRSA colonisation and infection has recently expanded to further ecological niches. Since the 1990s, an increasing incidence of MRSA infections arising in the community (community-associated methicillin-resistant *Staphylococcus aureus*, CA-MRSA) has been reported from many countries worldwide [3]. More recently, MRSA have been found to colonise or infect livestock and humans exposed to those animals in several countries. Such MRSA have been dubbed livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) [4]. Interactions between these different reservoirs for MRSA have been reported, including nosocomial infections by CA-MRSA [5,6] and importation of LA-MRSA into hospitals [7].

MRSA is amongst the most challenging infection control issues. In this review, we delineate the burden of MRSA disease in Europe across healthcare sectors and review the economic impact of MRSA infections. Finally, we outline threats due to recent changes in the epidemiology of MRSA and identify unmet needs regarding surveillance, prevention and control of MRSA in Europe.

Methods

We searched PubMed and supplemented this with articles from our personal archives to retrieve the literature for this review. For the PubMed search, a restriction to articles published between 2001 and 2009 and written in English was applied. Our review is structured in two sections: (i). Epidemiology and burden of MRSA infections, in which we outline the main determinants of MRSA disease burden, compared to infections by methicillin-susceptible *S. aureus* (MSSA), and summarise recent trends in the epidemiology of MRSA in Europe in healthcare facilities, the community and livestock; and (ii). Discussion on new reservoirs and control challenges, where, against the background of data described in the first section, we identify potential threats from the current epidemiology of MRSA in Europe and discuss perspectives for the prevention and control of MRSA in European countries.

Epidemiology and burden of MRSA infections

Burden of disease

Monitoring the epidemiology and the burden of MRSA infections in European countries is crucial. This has been underlined by the finding that MRSA does not just replace MSSA as a causative agent for infections, but frequently adds to the latter's disease burden, leading to a net increase in the incidence of *S. aureus* infections (Table 1) [8,9].

Moreover, it has been debated whether MRSA bacteraemia causes higher mortality than MSSA bacteraemia, e.g. due to vancomycin's inferiority in the treatment of deep-seated *S. aureus* infections, compared with semi-synthetic penicillins, compared with semi-synthetic penicillins used for MSSA [10]. Two meta-analyses have found an increased mortality risk of 1.93 (95% CI: 1.54 to 2.42) [10] and 2.03 (95% CI: 1.55 to 2.65) [11] associated with MRSA bacteraemia compared with MSSA. However, there is an ongoing discussion about methodological flaws of the studies included in these meta-analyses, e.g. with respect to whether they fully adjusted for appropriateness of therapy and severity of underlying diseases. Table 2 contains an update of additional (published between 2001 and 2009) regarding this issue: their results still do not clearly answer the initial question.

Besides effects on mortality, several studies mainly from the USA have indicated that MRSA infections cause a significant additional financial burden over

Table 1

Key elements in the recent epidemiology of MRSA infections in Europe

Characteristic	Summary
MRSA vs MSSA infections	Recent investigations indicate that: • MRSA adds to the total burden of *S. aureus* disease; • Invasive MRSA infections are associated with a higher mortality compared with MSSA; • MRSA infections generate extra costs of care mainly due to prolonged length of hospital stay.
Epidemiological reservoirs	In European countries, MRSA is associated with three main reservoirs: healthcare institutions (HA-MRSA), the community (CA-MRSA), and livestock (LA-MRSA).
HA-MRSA	According to the pan-European surveillance systems, EARSS and HELICS, the prevalence of HA-MRSA infection markedly varies between countries but has been decreasing in several over the past five years.
CA-MRSA	CA-MRSA infections have emerged in most European countries but are still less frequent overall than HA-MRSA infections.
LA-MRSA	In the majority of European countries, livestock is colonised with MRSA. The impact of this reservoir on public health is unclear.

CA-MRSA: community-associated methicillin-resistant *Staphylococcus aureus*; EARSS: European Antimicrobial Resistance Surveillance System; HA-MRSA: healthcare-associated methicillin-resistant *Staphylococcus aureus*; HELICS: Hospital in Europe Link for Infection Control through Surveillance; LA-MRSA: livestock-associated methicillin-resistant *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*.

Table 2

Estimates of mortality of MRSA bacteraemia compared with MSSA bacteraemia from studies published between 2001 and 2009*

Type, place and period of study	Number of patients with *S. aureus* infection (% of MRSA cases)	Percentage mortality in MRSA patients	Percentage mortality in MSSA patients	Odds ratio/hazard ratio for MRSA–associated mortality (95% CI)	Reference
Single-centre, university hospital, Taiwan, 1990–2004	1,148 (74)	50%[a]	28%[a]	1.78 (1.3–2.44)	Wang *et al.* [12]
Single-centre, university hospital, Belgium, 1992–1998	85 (44.7)	64%[b]	24%[b]	1.93 (1.18–3.18)	Blot *et al.* [13]
Single-centre, teaching hospital, UK, 1995–2000	815 (46.9)	12%[c]	5%[c]	1.72 (0.92–3.20)	Melzer *et al.* [14]
Veterans affairs healthcare system, USA, 1995–2003	438 (44)	34%[d]	20%[d]	1.8 (1.2–3.0)	Shurland *et al.* [15]
Single-centre, university hospital, USA, 1996–2001	143 (38)	35%[d]	12%[d]	5.4 (1.5–18.7)	Reed SD *et al.* [16]
Single-centre, university hospital, France, 1997–1998	99 (30)	43%[e]	20%[e]	2.97 (1.12–7.88)	Talon *et al.* [17]
Single-centre, tertiary–care teaching hospital, USA, 1997–2000	348 (28)	23%[f]	20%[f]	1.2 (0.68–2.12)	Cosgrove SE *et al.* [18]
Multi-centre, Germany, 1997–2002	378 (25.1)	17%[c]	6%[c]	3.84 (1.51–10.2)	Gastmeier *et al.* [19]
Two centres, teaching hospital UK, 1997–2004	461 (50)	34%[a]	27%[a]	1.49 (0.99–2.26)	Wyllie *et al.* [8]
Single-centre, teaching hospital, USA, 1999–2001	353 (48)	31%[a]	15%[a]	1.4 (0.7–3.0)	Lodise *et al.* [20]
Single-centre, teaching hospital, Brazil, 2000–2001	111 (55)	55%[a]	25%[a]	2.52 (0.96–6.6)	Guilarde *et al.* [21]
Single-centre, university hospital, Taiwan, 2001–2006	215 (14)	10%[a]	13%[a]	0.73 (0.21–2.60)	Wang *et al.* [22]
Single-centre, university hospital, Belgium, 2002–2004	154 (43)	42%[g]	24%[g]	3.04 (1.15–8.04)	Libert *et al.* [23]
Single-centre, university hospital, Germany, 2002–2007	521 (13)	42%[d]	19%[d]	2.6 (1.4–4.9)	Rieg *et al.* [24]
Single-centre, tertiary care, USA, 2004–2005	68 (53)	47%[h]	19%[h]	5.1 (1.1–22.9)i	Malani *et al.* [25]

CI: confidence interval; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; UK: United Kingdom; USA: United States of America.

[a] Thirty-day mortality.
[b] Mortality at the end of hospital stay.
[c] Time frame of mortality not provided.
[d] Ninety-day/12-week mortality.
[e] Fourteen-day mortality.
[f] Seven-day mortality.
[g] Bloodstream infection-related mortality.
[h] Six-month mortality.

Table 3

Estimates from recently published (2001–2009) studies of hospital financial burden associated with MRSA infections compared with MSSA infections

Type of infection, setting of study	Number of patients	Effect on hospital length of stay	Effects on costs	Reference
Bacteraemia, one teaching hospital, USA, 1997–2000	96 MRSA vs 252 MSSA	Median LOS: 9 days (MRSA) vs 7 days (MSSA), p=0.045; MRSA independent risk factor for increased LOS (1.3–fold, p=0.016)	Hospital charges after *S. aureus* bacteraemia: USD 26,424 (MRSA) vs USD 19,212 (MSSA), p=0.008	Cosgrove SE *et al.* [18]
Haemodialysis-related infections, one teaching hospital, USA, 1996–2001	54 MRSA vs 89 MSSA	Median LOS: 11d (MRSA) vs 7days (MSSA), p<0.001	Adjusted median costs for initial hospitalisation: USD 21,251 (MRSA) vs USD 13,978 (MSSA), p=0.012 and after 12 weeks: USD 25,518 (MRSA) vs USD 17,354 (MSSA), p=0.015	Reed SD *et al.* [16]
Surgical site infections, one tertiary care and one community hospital, USA, 1994–2000	121 MRSA vs 165 MSSA vs 193 uninfected controls	Median LOS after surgery: 5 days (uninfected) vs 14 days (MSSA) vs 23 days (MRSA), P<0.001. Median LOS after infection: 15 days (MRSA) vs 10 days (MSSA), P<0.001	Median costs for uninfected patients: USD 29,455 vs USD 92,363 (MRSA) vs USD 52,791 (MSSA), p<0.001	Engemann JJ *et al.* [26]
BSIs, one tertiary care hospital, USA, 2000–2003	95 MRSA vs 87 MSSA	LOS after infection: 10.5 days (MSSA) vs 20.5 days (MRSA), p=0.003; adjusted mean excess LOS ratio: 1.1 (95% CI, 0.8–1.4, not significant)	Median total hospital costs: USD 42,137 (MSSA) vs USD 113,852 (MRSA); adjusted mean excess cost ratio: 1.2 (95%CI, 0.9–1.6, not significant)	Ben–David D *et al.* [27]
Ventilator-associated pneumonia, 16 teaching and 43 nonteaching hospitals, USA, 2002–2003	95 MSSA vs 59 MRSA	Total inpatient LOS: 20 days (MRSA) vs 15d (MSSA), p=0.04. MRSA patients consumed excess resources of 3.8 inpatient days, p=0.08	Patients with MRSA–VAP consumed excess resources of USD 7731 (p=0.035) in total costs	Shorr AF *et al.* [28]

BSI: bloodstream infection; ICU: intensive care unit; LOS: length of stay; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; SSI: surgical site infection; USA: United States of America; USD: United States dollars; VAP: ventilator-associated pneumonia.

MSSA infections after adjustment for co-morbidities, which is largely the result of prolonged hospital stay and occupation of isolation rooms (Table 3).

Moreover, a Dutch study has recently estimated that the implementation of a MRSA 'search and destroy' policy was highly cost–effective in one hospital under investigation [29]. During the study period, no MRSA bacteraemia was observed in this hospital. Assuming that 50% of all nosocomial *S. aureus* would be MRSA, if no search and destroy strategy had been implemented the authors estimated 36 MRSA bacteraemia cases per year were thus avoided [29].

Furthermore, it has been found that MRSA carriers are at risk for MRSA infection, since up to 29% of persons colonised with MRSA subsequently develop MRSA morbidity [30,31]. For example, MRSA carriers in long-term care facilities have a 1.4-fold increased risk for mortality within 36 months [32] and 5% of long-term carriers have been shown to die because of an MRSA infection within four years of carriage [30].

Epidemiology of healthcare-associated MRSA

Nosocomial infections acquired by patients receiving institutional healthcare have long been the classical presentation of MRSA infections. Risk factors for MRSA acquisition include hospital care, care in chronic care facilities and nursing homes for elderly people, presence of indwelling devices or chronic wounds and previous antibiotic treatment.

The majority of HA-MRSA strains isolated in European countries have emerged from the introduction of the staphylococcal cassette chromosome *mec* (SCC*mec*) harbouring the methicillin-resistance gene *mec*A, into five *S. aureus* clonal complexes (CC), as defined by multi–locus sequence typing (MLST): CC5, CC8, CC22, CC30 and CC45 [3].

Recent data on the burden of HA-MRSA disease on a European scale are available from two surveillance systems supported by ECDC (EARSS, HELICS). The European Antimicrobial Resistance Surveillance System (EARSS) is used in most European countries to record the incidence of bloodstream and cerebrospinal MRSA infections, representing severe clinical courses of (mostly HA-) MRSA morbidity. As shown recently, hospitals contributing to EARSS provide care for about 20% of the EU population, accession countries and Israel [33]. However, EARSS coverage ranges between 5% and 100%, depending on the country, and therefore representative data from all countries are not available [33]. In 2008, the proportion of MRSA in *S. aureus* blood culture isolates was less than 5% in Denmark, Estonia, Finland, Iceland, the Netherlands, Norway and Sweden. In three countries (Austria, Luxembourg, Slovenia), a proportion of less than 10% was found, while in eight countries the proportion was between 10%-24% (Belgium, Czech Republic, France, Germany, Hungary, Latvia, Poland, Switzerland) In total, 13 countries reported a proportion equal to or above 25% (Bulgaria, Croatia, Cyprus, Greece, Israel, Italy, Malta, Portugal, Republic of Ireland, Romania, Spain, Turkey, United Kingdom) including two countries (Malta, Portugal) with proportions above 50% [33].

The attributable fraction of HAI caused by MRSA is documented by the EU-wide surveillance network of infections in intensive care units (ICUs), which was established under the name "HELICS". In 2007, the HELICS network (involving 13 European countries) reported that, of 54,574 patients staying in an ICU for more than two days, 6.2% acquired pneumonia. Overall, 17% of all cases of ICU-acquired pneumonia [34] were caused by *S. aureus*, 33% of which were MRSA. Moreover, ICU-acquired BSIs were caused by *S. aureus* in 11% of all 4,812 cases included in the report with an MRSA proportion of 42% [34].

According to EARSS 2008 data, a significant declining trend of invasive MRSA infections has been observed in Austria, Poland, Latvia, Romania, Italy, France, Belgium and the United Kingdom over the last four years of surveillance [33]. Likewise, there was a significant decrease in the mean incidence of ICU-acquired MRSA infection reported via HELICS between 2004 and 2007 [34]. These trends illustrate that many European countries have experienced successes in the prevention and control of MRSA in the healthcare setting as indicated by either continuously low incidence rates or recently decreasing rates of MRSA infections.

Epidemiology of community-associated MRSA

Until the 1990s, infections due to MRSA were rarely observed in the community. Since then, a rapid emergence of CA-MRSA was first reported from Australia and the USA, where outbreaks were described amongst underprivileged aboriginal communities, schoolchildren, prison inmates, soldiers, athletes and men who have sex with men [35]. These communities have not been reported so far as major reservoirs for CA-MRSA in Europe. Risk factors for the development of CA-MRSA infection include close contact with other people with CA-MRSA, e.g. having a family member from a country with a high prevalence of CA-MRSA, living in crowded facilities, poor hygiene, sharing of personal items and performing contact sports [36,37]. These observations help to elucidate the spread of MRSA outside healthcare settings. So far, the most important risk factor for CA-MRSA infections in many European countries is travel to countries with a higher prevalence of CA-MRSA [38-40].

CA-MRSA causes mainly skin- and soft-tissue infections ranging in severity from furuncles to necrotising fasciitis [37]. Moreover, the description of serious invasive CA-MRSA infections, such as necrotising pneumonia, is cause for concern, because these infections are associated with a lethality of up to 75% [41].

The epidemic rise in CA-MRSA infections in the USA was mainly due to the successful spread of an MRSA strain associated with the pulsed-field gel electrophoresis (PFGE) profile USA300 within the MLST ST8/SCC*mec* IV clone and harbouring the *lukS-lukF* genes, encoding the Panton-Valentine leukocidin (PVL) [35]. Other clones have contributed to this epidemic to a lesser extent [3].

In several European countries, infections due to the predominant USA clone (USA300/ST8) have also been reported [39,42-44]. However, the spread of this clone seems hitherto limited in Europe where other PVL-positive CA-MRSA clones, especially ST80/to44/SCC*mec* IV, are also prevalent [3,46].

Defining the overall burden of CA-MRSA in European countries and comparing proportions of CA-MRSA among all MRSA isolates between different studies is hindered by differences in the definitions used [37]. However, the proportion of CA-MRSA with respect to total MRSA is reported to range between 1% and 2% in Spain and Germany [42,43] and 29–56% in Denmark and Sweden, partly reflecting the low prevalence of HA-MRSA in these Scandinavian countries [47,48]. Among outpatients with *S. aureus* infections, MRSA accounted for 6% in the Ligurian region in Italy [49], 14% in Germany [50], 18% in France [51] and 30% in Greece [52].

Epidemiology of livestock-associated MRSA

Recently, it has been found that the burden of MRSA colonisation and infection also involves animals, particularly livestock. In Europe, a recent survey published by the European Food Safety Authority (EFSA) identified MRSA in pig holdings of 17 EU Member States [53]. The MRSA clone, which was isolated from the vast majority of pigs, was non-typeable by PFGE after *Sma*I digestion – due to DNA methylation not, however, affecting the *Sma*I isoschizomer *Cfr*9I [54] – was tetracycline-resistant, and belonged to MLST CC398 [53].Besides swine, MRSA CC398 strains have also been detected in other animals such as cattle [55] and poultry [4]. Although the animals are mostly colonised by MRSA, infections have been described in pigs [56] and horses [57].

The impact of a livestock reservoir for humans is currently under investigation. Whereas 23–38% of persons having contact with MRSA-positive pigs or veal calves were colonised with MRSA [7,58,59], only 4% of their family members, who had no direct exposure to the animals, were colonised in one study [60]. In areas with a high density of MRSA CC398-positive swine, this clone can influence the MRSA epidemiology markedly in healthcare settings. For instance, it has led to a three-fold increase in MRSA incidence over a few years in a Dutch hospital located in a pig-dense area [7], and, in a German hospital situated in a region with intense livestock farming, 22% of MRSA patients colonised with MRSA at hospital admission carried it [61].

This continuous import of MRSA CC398 from an animal reservoir into hospitals can result in nosocomial spread of MRSA to patient groups susceptible to the development of MRSA infections [44]. Nosocomial transmission of MRSA CC398 has indeed been reported [62]. Moreover, this strain has caused severe human infections such as endocarditis, soft-tissue infections and ventilator-associated pneumonia [63-65].

Nevertheless, the burden of human infections caused by MRSA CC398 in Europe remains poorly understood. The proportion of MRSA CC398 among all MRSA ranges from 0.3% in Germany [65] to 41% in the Netherlands [66]. Matters of further concern include the facts that PVL-encoding genes have been detected in a few MRSA CC398 isolates [67] and a *cfr* plasmid conferring resistance against oxazolidinones was found in an MRSA CC398 background [68].

Another potential human health threat is related to food contamination with MRSA, which was documented by a Dutch study in 11.9% of retail meat products from several animal species, including beef (10.6%), pork (10.7%) and chicken (16%) [69]; detection by use of enrichment cultures only suggests low quantity contamination. The majority of these isolates belonged to the CC398 lineage, with only 15% to other clonal lineages [69]. To date, two outbreaks of human disease have been related to the consumption of MRSA-contaminated meat, one as a classical food intoxication [70] and the other with contaminated food as the source of nosocomial transmission [71]. Both were caused by non-CC398 MRSA strains. Thus, presently, food does not seem to be an important source for MRSA transmission or infection.

New reservoirs and control challenges

The recently decreasing or maintained low-level incidence of HA-MRSA in BSIs in many European countries [33] is encouraging. In a majority of countries, these successes can be linked to the implementation of multi–faceted preventive interventions (including measures focussing on screening, contact precautions, decolonisation, antibiotic stewardship, or bundles of preventive measures and care). In France, a national hospital infection control programme has been initiated and developed over 16 years, resulting in a 30% reduction of surgical site infections and a 20% decrease in MRSA rates from blood cultures [72]. In Belgium, a sustained decrease in the incidence of HA-MRSA infections was recorded between 2004 and 2008, measureable as a decrease in the mean proportion of MRSA of *S. aureus* (30–25%) and a decrease in the median incidence of nosocomial MRSA (3.2 to 1.6 per 100 admissions) [73]. This success has been achieved by a multi–faceted approach, including the update and strengthening of national MRSA guidelines, the extension of prospective surveillance and screening activities [74], and activities to promote the prudent use of antibiotics [75]. In England, a governmental reduction target in MRSA bacteraemia was set in 2004, demanding halving the

number of MRSA isolated from blood cultures by 2008, against the baseline of 2003–2004. In order to achieve this aim, a bundle of measures was consecutively implemented in English hospitals, including the mandatory reporting of all MRSA bacteraemia by the hospital chief executive officers, public benchmarking of MRSA incidence rates, the production of guidance on preventing HAIs, the establishment of a national hand hygiene campaign, prudent use of antibiotics, and the implementation of so called 'high impact interventions', i.e. care bundles focussing on key clinical procedures that can increase the risk of infection if not performed appropriately (e.g. central venous catheter care) [76]. After five years, data confirm a 62% reduction in the incidence of MRSA from blood cultures in England [77].

To what extent the multi–faceted approaches linked to the decreasing trends in MRSA infections in these countries can serve as examples of good practice for planning and implementing national control interventions in other EU countries with different healthcare structures and resource attribution, remains to be seen.

Nevertheless, the burden of HA-MRSA extends beyond acute care hospitals to long-term care facilities (LCTFs), such as nursing homes. This has been underlined in several studies showing high prevalence rates of MRSA carriage among LTCF residents and marked rate variation between nursing homes and regions in Belgium (2–43%) [78], Germany (1%) [79], Spain (16%) [80], France (38%) [81] and the UK (5–23%) [82,83]. Despite this variation, in the majority of cases, the clonal structure of MRSA isolates from nursing home residents was closely related to that found among patients in neighbouring acute care hospitals [78]. In addition, a recent study has shown that within six weeks after discharge from a hospital, less than 14% of LTCF residents are readmitted [84], which highlights that an appreciable percentage of patients circulates between hospital and LTCF several times per year. Consequently, effective MRSA containment in the healthcare setting cannot be limited to acute care hospitals, but must include LCTFs also. Otherwise, the significant MRSA reservoir that has developed in LTCFs and the transmission dynamics between LTCFs and acute care hospitals due to the transfer of patients is bound to compromise control. That this problem may be underestimated is indeed suggested by an admittedly limited number of published investigations [85].

A second challenge concerns CA-MRSA which has now emerged across Europe. Although its prevalence is still considerably lower than in the USA, the number of CA-MRSA infections appears to be increasing, especially in those European countries where the incidence of HA-MRSA is low and surveillance of MRSA more extensive [30,31]. The problem of CA-MRSA infections is not limited to the community but also affects nosocomial infections due to the introduction of CA-MRSA in healthcare settings [86,87]. In addition, only a limited number of European countries have developed national strategies and no common European strategy has yet been developed for the surveillance or the prevention of CA-MRSA spread.

The final challenge to tackle is the animal MRSA reservoir. Despite the EU-wide spread of MRSA in pigs, its implications for humans directly or indirectly exposed to livestock and for patients attending healthcare institutions located in farming areas remain unclear. Although epidemic spread of LA-MRSA among persons without direct contact to animals is rare, and the burden of human infections caused by LA-MRSA strains is still lower than that observed for CA-MRSA, infection control guidelines in many European countries should address the potential risk of acquiring MRSA via contact with livestock farming.

Conclusions

MRSA infections constitute an important and still evolving public health challenge for European countries. Successful MRSA control in some countries and facilities offers opportunities for identifying effective interventions and reassessment of best practice. In contrast, the rapid emergence of MRSA in the community and in livestock underpins the fact that MRSA transmission can occur in everyday life, in home care, during travel, leisure activities, cross-border commuting,

Table 4

Controlling MRSA: public health challenges and perspectives

Objective	Need for improvement
Strengthening prevention and control of HA-MRSA	Systematic assessment of effectiveness of MRSA control strategies and review of national guidelines for MRSA prevention and control
Control of emerging threats	Guidance on the prevention and control of CA-MRSA, LA-MRSA and HA-MRSA in long-term care facilities
Intersectoral coordination	Coordinated actions to control the spread of MRSA between different healthcare sectors (hospitals, long-term care facilities, ambulatory care) and veterinary care
European healthcare cooperation	European-wide concerted actions to control cross-border MRSA spread

CA-MRSA: community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA: healthcare-associated methicillin-resistant *Staphylococcus aureus*; LA-MRSA: livestock-associated methicillin-resistant *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

exposure to contaminated food samples or livestock transport. For long-term success in controlling MRSA, coordinated actions between different healthcare sectors (acute, long-term, ambulatory) and veterinary care are warranted and concerted efforts at European level will be of increasing importance. These efforts should begin with an agreement upon definitions for CA- and LA-MRSA and continue with the improvement of evidence-based guidance and the implementation of preventive measures to result in better prevention and control of MRSA in Europe (Table 4).

* Erratum: by mistake, a wrong table (Table 2) was posted with the original article. We apologise for this error and corrected it on 15 October 2010.

References

1. Council of the European Union. Council recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare-associated infections (2009/C151/01). Official Journal of the European Union. 3 Jul 2009. Available from: http://ec.europa.eu/health/patient_safety/docs/council_2009_en.pdf
2. European Centre for Disease Prevention and Control/European Medicines Agency (ECDC/EMEA). Joint technical report The bacterial challenge: time to react. Stockholm:ECDC/EMEA; 2009. Available from: http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf
3. Deurenberg RH, Vink C, Kalenic S, Friedrich AW, Bruggeman CA, Stobberingh EE. The molecular evolution of methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect. 2007;13(3):222-35.
4. Nemati M, Hermans K, Lipinska U, Denis O, Deplano A, Struelens M, et al. Antimicrobial resistance of old and recent Staphylococcus aureus isolates from poultry: first detection of livestock-associated methicillin-resistant strain ST398. Antimicrob Agents Chemother. 2008;52(10):3817-9.
5. Moore CL, Hingwe A, Donabedian SM, Perri MB, Davis SL, Haque NZ, et al. Comparative evaluation of epidemiology and outcomes of methicillin-resistant Staphylococcus aureus (MRSA) USA300 infections causing community- and healthcare-associated infections. Int J Antimicrob Agents. 2009;34(2):148-55.
6. Skov RL, Jensen KS. Community-associated meticillin-resistant Staphylococcus aureus as a cause of hospital-acquired infections. J Hosp Infect. 2009;73(4):364-70.
7. van Rijen MM, Van Keulen PH, Kluytmans JA. Increase in a Dutch hospital of methicillin-resistant Staphylococcus aureus related to animal farming. Clin Infect Dis. 2008;46(2):261-3.
8. Wyllie DH, Crook DW, Peto TE. Mortality after Staphylococcus aureus bacteremia in two hospitals in Oxfordshire, 1997-2003: cohort study. BMJ. 2006;333(7562):281.
9. Stamm AM, Long MN, Belcher B. Higher overall nosocomial infection rate because of increased attack rate of methicillin-resistant Staphylococcus aureus. Am J Infect Control. 1993;21(2):70-4.
10. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis. 2003;36(1):53-9.
11. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant Staphylococcus aureus bacteremia: a meta-analysis. Med J Aust. 2001;175(5):264-7.
12. Wang F, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. Am J Infect Control. 2008;36(2):118-22.
13. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Arch Intern Med. 2002;162(19):2229-35.
14. Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant Staphylococcus aureus more virulent than methicillin-susceptible S. aureus? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis. 2003;37(11):1453-60.
15. Shurland S, Zhan M, Bradham DD, Roghmann M. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible Staphylococcus aureus. Infect Control Hosp Epidemiol. 2007;28(3):273-9.
16. Reed SD, Friedman JY, Engemann JJ, Griffiths RI, Anstrom KJ, Kaye KS, et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol. 2005;26(2):175-83.
17. Talon D, Woronoff-Lemsi MC, Limat S, Bertrand X, Chatillon M, Gil H, et al. The impact of resistance to methicillin in Staphylococcus aureus bacteremia on mortality. Eur J Intern Med. 2002;13(1):31-36.
18. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol. 2005;26(2):166-74.
19. Gastmeier P, Sohr D, Geffers C, Behnke M, Daschner F, Ruden H. Mortality risk factors with nosocomial Staphylococcus aureus infections in intensive care units: results from the German Nosocomial Infection Surveillance System (KISS). Infection. 2005;33(2):50-5.
20. Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with Staphylococcus aureus bacteremia. Diagn Microbiol Infect Dis. 2005;52(2):113-22.
21. Guilarde AO, Turchi MD, Martelli CMT, Primo MG. Staphylococcus aureus bacteremia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. J Hosp Infect. 2006;63(3):330-6.
22. Wang JL, Chen SY, Wang JT, Wu GH, Chiang WC, Hsueh PR, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant Staphylococcus aureus and methicillin-susceptible S. aureus. Clin Infect Dis. 2008;46(6):799-806.
23. Libert M, Elkholti M, Massaut J, Karmali R, Mascart G, Cherifi S. Risk factors for meticillin resistance and outcome of Staphylococcus aureus bloodstream infection in a Belgian university hospital. J Hosp Infect. 2008;68(1):17-24.
24. Rieg S, Peyerl-Hoffmann G, de With K, Theilacker C, Wagner D, Hubner J, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation--a study of 521 patients in Germany. J Infect. 2009;59(4):232-9.
25. Malani PN, Rana MM, Banerjee M, Bradley SF. Staphylococcus aureus bloodstream infections: the association between age and mortality and functional status. J Am Geriatr Soc. 2008;56(8):1485-9.
26. Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis. 2003;36(5):592-8.
27. Ben-David D, Novikov I, Mermel LA. Are there differences in hospital cost between patients with nosocomial methicillin-resistant Staphylococcus aureus bloodstream infection and those with methicillin-susceptible S. aureus bloodstream infection? Infect Control Hosp Epidemiol. 2009;30(5):453-60.
28. Shorr AF, Tabak YP, Gupta V, Johannes RS, Liu LZ, Kollef MH. Morbidity and cost burden of methicillin-resistant Staphylococcus aureus in early onset ventilator-associated pneumonia. Crit Care. 2006;10(3):R97.
29. van Rijen MM, Kluytmans JA. Costs and benefits of the MRSA Search and Destroy policy in a Dutch hospital. Eur J Clin Microbiol Infect Dis. 2009;28(10):1245-52.
30. Datta R, Huang SS. Risk of infection and death due to methicillin-resistant Staphylococcus aureus in long-term carriers. Clin Infect Dis. 2008;47(2):176-81.
31. Huang SS, Platt R. Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization. Clin Infect Dis. 2003;36(3):281-5.
32. Suetens C, Niclaes L, Jans B, Verhaegen J, Schuermans A, Van Eldere J, et al. Methicillin-resistant Staphylococcus aureus colonization is associated with higher mortality in nursing home residents with impaired cognitive status. J Am Geriatr Soc. 2006;54(12):1854-60.
33. European Antimicrobial Resistance Surveillance System (EARSS). EARSS Annual Report 2008. Bilthoven:EARSS; 2009. [Accessed 14 Jun 2010]. Available from: http://www.rivm.nl/earss/Images/EARSS%202008_final_tcm61-65020.pdf
34. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report on communicable diseases in Europe 2009. Stockholm:ECDC; 2010. [Accessed 14 Jun 2010]. Available from: http://www.ecdc.europa.eu/en/publications/Publications/ 0910_SUR_Annual_Epidemiological_Report_on_Communicable_Diseases_in_Europe.pdf

35. Tenover FC, Goering RV. Methicillin-resistant Staphylococcus aureus strain USA300: origin and epidemiology. J Antimicrob Chemother. 2009;64(3):441-6.
36. Ellington MJ, Perry C, Ganner M, Warner M, McCormick S, Hill RL, et al. Clinical and molecular epidemiology of ciprofloxacin-susceptible MRSA encoding PVL in England and Wales. Eur J Clin Microbiol Infect Dis. 2009; 28(9):1113-21.
37. Diederen BM, Kluytmans JA. The emergence of infections with community-associated methicillin resistant Staphylococcus aureus. J Infect. 2006;52(3):157-68.
38. Denis O, Deplano A, De Beenhouwer H, Hallin M, Huysmans G, Garrino MG, et al. Polyclonal emergence and importation of community-acquired methicillin-resistant Staphylococcus aureus strains harbouring Panton-Valentine leucocidin genes in Belgium. J Antimicrob Chemother. 2005;56(6):1103-6.
39. Larsen AR, Stegger M, Goering R, Sørum M, Skov R. Emergence and dissemination of the methicillin resistant Staphylococcus aureus USA300 clone in Denmark (2000-2005). Euro Surveill. 2007;12(2):pii=682. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=682
40. Bocher S, Gervelmeyer A, Monnet DL, Molbak K, Skov RL, Danish CA-MRSA Study Group. Methicillin-resistant Staphylococcus aureus: risk factors associated with community-onset infections in Denmark. Clin Microbiol Infect. 2008;14(10):942-8.
41. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, et al. Association between Staphylococcus aureus strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet. 2002;359(9308):753-9.
42. Witte W, Strommenger B, Cuny C, Heuck D, Nuebel U. Methicillin-resistant Staphylococcus aureus containing the Panton-Valentine leucocidin gene in Germany in 2005 and 2006. J Antimicrob Chemother. 2007;60(6):1258-63.
43. Manzur A, Dominguez AM, Pujol M, Gonzalez MP, Limon E, Hornero A, et al. Community-acquired methicillin-resistant Staphylococcus aureus infections: an emerging threat in Spain. Clin Microbiol Infect. 2008;14(4):377-80.
44. Bartels MD, Boye K, Rhod Larsen A, Skov R, Westh H. Rapid increase of genetically diverse methicillin-resistant Staphylococcus aureus, Copenhagen, Denmark. Emerg Infect Dis. 2007;13(10):1533-40.
45. Ruppitsch W, Stoger A, Schmid D, Fretz R, Indra A, Allerberger F, et al. Occurrence of the USA300 community-acquired Staphylococcus aureus clone in Austria. Euro Surveill. 2007;12(10):E071025.1.
46. Goering RV, Larsen AR, Skov R, Tenover FC, Anderson KL, Dunman PM. Comparative genomic analysis of European and Middle Eastern community-associated methicillin-resistant Staphylococcus aureus (CC80:ST80-IV) isolates by high-density microarray. Clin Microbiol Infect. 2009; 15(8):748-55.
47. Larsen AR, Stegger M, Bocher S, Sorum M, Monnet DL, Skov RL. Emergence and characterization of community-associated methicillin-resistant Staphyloccocus aureus infections in Denmark, 1999 to 2006. J Clin Microbiol. 2009;47(1):73-8.
48. Fang H, Hedin G, Li G, Nord CE. Genetic diversity of community-associated methicillin-resistant Staphylococcus aureus in southern Stockholm, 2000-2005. Clin Microbiol Infect. 2008;14(4):370-6.
49. Marchese A, Gualco L, Maioli E, Debbia E. Molecular analysis and susceptibility patterns of meticillin-resistant Staphylococcus aureus (MRSA) strains circulating in the community in the Ligurian area, a northern region of Italy: emergence of USA300 and EMRSA-15 clones. Int J Antimicrob Agents. 2009;34(5):424-8.
50. Jappe U, Heuck D, Strommenger B, Wendt C, Werner G, Altmann D, et al. Staphylococcus aureus in dermatology outpatients with special emphasis on community-associated methicillin-resistant strains. J Invest Dermatol. 2008;128(11):2655-64.
51. Thibaut S, Caillon J, Huart C, Grandjean G, Lombrail P, Potel G, et al. Susceptibility to the main antibiotics of Escherichia coli and Staphylococcus aureus strains identified in community acquired infections in France (MedQual, 2004-2007). Med Mal Infect. 2010;40(2):74-80.
52. Vourli S, Vagiakou H, Ganteris G, Orfanidou M, Polemis M, Vatopoulos A, et al. High rates of community-acquired, Panton-Valentine leukocidin (PVL)- positive methicillin-resistant S. aureus (MRSA) infections in adult outpatients in Greece. Euro Surveill. 2009;14(2):pii=19089. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19089
53. European Food Safety Authority (EFSA). Analysis of the baseline survey on the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in holdings with breeding pigs, in the EU, 2008 - Part A: MRSA prevalence estimates. EFSA Journal 2009;7(11):1376.
54. Bosch T, de Neeling AJ, Schouls LM, van der Zwaluw KW, Kluytmans JA, Grundmann H, et al. PFGE diversity within the methicillin-resistant Staphylococcus aureus clonal lineage ST398. BMC Microbiol. 2010;10:40.
55. Monecke S, Kuhnert P, Hotzel H, Slickers P, Ehricht R. Microarray based study on virulence-associated genes and resistance determinants of Staphylococcus aureus isolates from cattle. Vet Microbiol. 2007;125(1-2):128-40.
56. Schwarz S, Kadlec K, Strommenger B. Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius detected in the BfT-GermVet monitoring programme 2004-2006 in Germany. J Antimicrob Chemother. 2008;61(2):282-5.
57. Cuny C, Strommenger B, Witte W, Stanek C. Clusters of infections in horses with MRSA ST1, ST254, and ST398 in a veterinary hospital. Microb Drug Resist. 2008;14(4):307-10.
58. Voss A, Loeffen F, Bakker J, Klaassen C, Wulf M. Methicillin-resistant Staphylococcus aureus in pig farming. Emerg Infect Dis. 2005;11(12):1965-6.
59. Denis O, Suetens C, Hallin M, Catry B, Ramboer I, Dispas M, et al. Methicillin-resistant Staphylococcus aureus ST398 in swine farm personnel, Belgium. Emerg Infect Dis. 2009;15(7):1098-101.
60. Cuny C, Nathaus R, Layer F, Strommenger B, Altmann D, Witte W. Nasal colonization of humans with methicillin-resistant Staphylococcus aureus (MRSA) CC398 with and without exposure to pigs. PLoS One. 2009;4(8):e6800.
61. Köck R, Harlizius J, Bressan N, Laerberg R, Wieler LH, Witte W, et al. Prevalence and molecular characteristics of methicillin-resistant Staphylococcus aureus (MRSA) among pigs on German farms and import of livestock-related MRSA into hospitals. Eur J Clin Microbiol Infect Dis. 2009;28(11):1375-82.
62. Wulf MW, Markestein A, van der Linden FT, Voss A, Klaassen C, Verduin CM. First outbreak of methicillin-resistant Staphylococcus aureus ST398 in a Dutch hospital, June 2007. Euro Surveill. 2008;13(9):pii=8051. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8051
63. Ekkelenkamp MB, Sekkat M, Carpaij N, Troelstra A, Bonten MJM. [[Endocarditis due to meticillin-resistant Staphylococcus aureus originating from pigs]. Ned Tijdschr Geneeskd. 2006;150(44):2442-7. Dutch.
64. Pan A, Battisti A, Zoncada A, Bernieri F, Boldini M, Franco A, et al. Community-acquired methicillin-resistant Staphylococcus aureus ST398 infection, Italy. Emerg Infect Dis. 2009;15(5):845-7.
65. Witte W, Strommenger B, Stanek C, Cuny C. Methicillin-resistant Staphylococcus aureus ST398 in humans and animals, Central Europe. Emerg Infect Dis. 2007;13(2):255-8.
66. Dutch Working Party on Antibiotic Policy (SWAB). NethMap 2008, Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands, 2009. Amsterdam:SWAB. [Accessed 14 Jun 2010]. Available from: http://www.swab.nl/swab/cms3.nsf/uploads/6E11368E7BB72739C12575940049664D/$FILE/NethMap_2008.pdf
67. Welinder-Olsson C, Floren-Johansson K, Larsson L, Oberg S, Karlsson L, Ahren C. Infection with Panton-Valentine leukocidin-positive methicillin-resistant Staphylococcus aureus t034. Emerg Infect Dis. 2008;14(8):1271-2.
68. Kehrenberg C, Cuny C, Strommenger B, Schwarz S, Witte W. Methicillin-resistant and -susceptible Staphylococcus aureus strains of clonal lineages ST398 and ST9 from swine carry the multidrug resistance gene cfr. Antimicrob Agents Chemother. 2009;53(2):779-81.
69. de Boer E, Zwartkruis-Nahuis JT, Wit B, Huijsdens; XW, de Neeling AJ, Bosch T, et al. Prevalence of methicillin-resistant Staphylococcus aureus in meat. Int J Food Microbiol. 2009; 134(1-2):52-6.
70. Jones TF, Kellum ME, Porter SS, Bell M, Schaffner W. An outbreak of community-acquired foodborne illness caused by methicillin-resistant Staphylococcus aureus. Emerg Infect Dis. 2002;8(1):82-4.
71. Kluytmans J, van Leeuwen W, Goessens W, Hollis R, Messer S, Herwaldt L, et al. Food-initiated outbreak of methicillin-resistant Staphylococcus aureus analyzed by pheno- and genotyping. J Clin Microbiol. 1995;33(5):1121-8.
72. Carlet J, Astagneau P, Brun-Buisson C, Coignard B, Salomon V, Tran B, et al. French national program for prevention of healthcare-associated infections and antimicrobial resistance, 1992-2008: positive trends, but perseverance needed. Infect Control Hosp Epidemiol. 2009;30(8):737-45.
73. Scientific Institute of Public Health. National Surveillance of Hospital Infections (NSIH). National Surveillance of Nosocomial Septicemia (Hospital-wide). National Analysis. Data from 1/01/2008 to 31/12/2008. Brussels: NSIH; 30 Jun 2009. Available from: http://www.iph.fgov.be/nsih/download/SEP/sBelg_2008_data.pdf.

74. Conseil Supérieur d' Hygiène. Guidelines for the control and prevention of methicillin-resistant Staphylococcus aureus transmission in Belgian hospitals [Accessed 14 Jun 2010]. Available from: https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DOCS/7725%20MRSA%20EN%202003.PDF

75. Goossens H, Coenen S, Costers M, De Corte S, De Sutter A, Gordts B, et al. Achievements of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). Euro Surveill. 2008;13(46):pii=19036. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19036

76. Department of Health (DH) [Internet]. London:DH. [Accessed 14 Jun 2010]. Available from: http://www.dh.gov.uk

77. Health Protection Agency (HPA). Healthcare-associated Infections in England: 2008-2009 Report. London:HPA; Reviewed 10 Sept 2009. [Accessed 14 Oct 2010]. Available from: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1252326222452

78. Denis O, Jans B, Deplano A, Nonhoff C, De Ryck R, Suetens C, et al. Epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) among residents of nursing homes in Belgium. J Antimicrob Chemother. 2009;64(6):1299-306.

79. von Baum H, Schmidt C, Svoboda D, Bock-Hensley O, Wendt C. Risk factors for methicillin-resistant Staphylococcus aureus carriage in residents of German nursing homes. Infect Control Hosp Epidemiol. 2002;23(9):511-5.

80. Manzur A, Gavalda L, Ruiz de Gopegui E, Mariscal D, Dominguez MA, Perez JL, et al. Prevalence of methicillin-resistant Staphylococcus aureus and factors associated with colonization among residents in community long-term-care facilities in Spain. Clin Microbiol Infect. 2008;14(9):867-72.

81. Eveillard M, Charru P, Rufat P, Hippeaux M, Lancien E, Benselama F, et al. Methicillin-resistant Staphylococcus aureus carriage in a long-term care facility: hypothesis about selection and transmission. Age Ageing. 2008;37(3):294-9.

82. Cox RA, Bowie PE. Methicillin-resistant Staphylococcus aureus colonization in nursing home residents: a prevalence study in Northamptonshire. J Hosp Infect. 1999;43(2):115-22.

83. Baldwin NS, Gilpin DF, Hughes CM, Kearney MP, Gardiner DA, Cardwell C, et al. Prevalence of methicillin-resistant Staphylococcus aureus colonization in residents and staff in nursing homes in Northern Ireland. J Am Geriatr Soc. 2009;57(4):620-6.

84. Ahearn DJ, Jackson TB, McIlmoyle J, Weatherburn AJ. Improving end of life care for nursing home residents: an analysis of hospital mortality and readmission rates. Postgrad Med J. 2010;86(1013):131-5.

85. Manzur A, Gudiol F. Methicillin-resistant Staphylococcus aureus in long-term-care facilities. Clin Microbiol Infect. 2009;15 (Suppl 7)(26-30).

86. D'Agata EM, Webb GF, Horn MA, Moellering RC Jr., Ruan S. Modeling the invasion of community-acquired methicillin-resistant Staphylococcus aureus into hospitals. Clin Infect Dis. 2009;48(3):274-84.

87. Webb GF, Horn MA, D'Agata EM, Moellering RC, Ruan S. Competition of hospital-acquired and community-acquired methicillin-resistant Staphylococcus aureus strains in hospitals. J Biol Dyn. 2009;48:271.

Letter to the editor. Spotlight on measles 2010: Measles in healthcare workers – vaccination should be revisited

E Botelho-Nevers[1], L Chevereau[1], P Brouqui (philippe.brouqui@univmed.fr)[1]
1. Pôle de Maladies Infectieuses, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, France

Citation style for this article:
Botelho-Nevers E, Chevereau L, Brouqui P. Letter to the editor. Spotlight on measles 2010: Measles in healthcare workers – vaccination should be revisited. Euro Surveill. 2010;15(41):pii=19687. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19687

Article published on 14 October 2010

To the editor: In the light of the current outbreak of measles in France reported by Parent du Chatelet *et al.* [1], we would like to report a case of hospital-acquired measles in a nurse who had not received the measles-mumps-rubella (MMR) vaccine. Working in our department of infectious diseases, she was infected in spite of barrier measures.

On 8 August 2010 a woman in her 20s was admitted to our department with a maculopapular rash associated with high-grade fever and cough. The cause was rapidly laboratory-confirmed as measles. From the moment of her admission in our ward to her discharge on 13 August she was confined to a single room and respiratory isolation measures were in place. As of 9 August, a nurse in her 20s took care of the patient using protective personal equipment including an FFP2 facial mask and alcohol-based hand rub.

Thirteen days after the first contact with the patient, the nurse presented with fever and four days later developed a maculopapular rash. She was laboratory-confirmed with measles which was complicated by keratitis. Following a 15-day sick leave the nurse recovered. She had had no contact with a case of measles in the community. A survey of other members of staff and patients in contact with the nurse was carried out. No other secondary cases of measles were described. One medical student without immunity to measles was vaccinated. It was not possible to establish a molecular link between the viruses in our two cases as all the measles virus genotypes circulating during the current local outbreak were identical.

The case reported here is noteworthy because an unvaccinated nurse trained in infectious diseases contracted measles in spite of efficient use of respiratory protective measures and alcohol-based hand rub. A recrudescence of measles is currently occurring in France, especially among children and young adults, due to insufficient vaccine coverage in these population groups [1]. Consequently young healthcare workers (HCW) are at risk of occupational measles if they are not immunised. In the literature, nosocomial transmission of measles from HCW to patients and from patients to unimmunised HCW has been reported [2,3]. Indeed measles is a highly contagious disease with a basic reproduction number ranging from 7.7 to 15 [4], as the transmission airborne droplets leads to a high risk of infection for unvaccinated or not naturally immunised individuals even if isolation measures are correctly applied. Vaccination is the only reliable protection against nosocomial spread of measles. Reports of susceptibility to measles showed a high level of immunity, including natural immunity, among HCW in Europe[5]. Therefore, even if the prevalence of non-immune HCW seems to be low, the low uptake of MMR immunisation and the increase in measles outbreaks [1] may increase the risk of nosocomial transmission. .

It should be mandatory to identify non-immune HCW and offer them vaccination. Only HWC who are vaccinated or willing to be vaccinated should be recruited to work on medical wards, especially high risk wards such as infectious disease, emergency room, paediatric, maternity and oncology wards. This recommendation should also extend to medical students who are often poorly protected against vaccine-preventable diseases as seen in our case.

If mandatory vaccination is not possible in France as we saw during the 2009 influenza pandemic, a strategy of voluntary vaccination for HCW should be rapidly implemented in hospitals, especially in high risk areas and even on infectious disease wards where isolation barriers are usually used carefully.

References

1. Parent du Châtelet I, Antona D, Freymuth F, Muscat M, Halftermeyer-Zhou F, Maine C, Floret D, Lévy-Bruhl D. Spotlight on measles 2010: Update on the ongoing measles outbreak in France, 2008-2010. Euro Surveill. 2010;15(36):pii=19656. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19656
2. Tafuri S, Germinario C, Rollo M, Prato R. Occupational risk from measles in healthcare personnel: a case report. J Occup Health. 2009;51(1):97-9.
3. Grgic-Vitek M, Frelih T, Ucakar V, Prosenc K, Tomažič J, Petrovec M, Kraigher A. Spotlight on measles 2010: A cluster of measles in a hospital setting in Slovenia, March 2010. Euro Surveill. 2010;15(20):pii=19573. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19573
4. Mossong J, Muller CP. Estimation of the basic reproduction number of measles during an outbreak in a partially vaccinated population. Epidemiol Infect. 2000;124(2):273-8.
5. Fedeli U, Zanetti C, Saia B. Susceptibility of healthcare workers to measles, mumps rubella and varicella. J Hosp Infect. 2002;51(2):133-5.

Authors' reply. Spotlight on measles 2010: Measles in healthcare workers – vaccination should be revisited

I Parent du Châtelet (i.parent@invs.sante.fr)[1], D Floret[2], J M Thiolet[1], D Lévy-Bruhl[1]
1. Institut de Veille Sanitaire (InVS, French Institute for Public Health Surveillance), Saint-Maurice, France
2. Claude Bernard Lyon 1 University, French working group on measles and congenital rubella elimination, Lyon, France

Citation style for this article:
Parent du Châtelet I, Floret D, Thiolet JM, Lévy-Bruhl D. Authors' reply. Spotlight on measles 2010: Measles in healthcare workers – vaccination should be revisited. Euro Surveill. 2010;15(41):pii=19685. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19685

Article published on 14 October 2010

To the editor: We thank Botelho-Nevers *et al.* for their interest in our paper [1] and for illustrating the risk for non-immune healthcare workers (HCWs) of contracting the disease in a context of high measles virus circulation in the community [2].

Since the beginning of the outbreak in 2008 and through the national early warning system [3], the French Institute for Public Health Surveillance (InVS) received a total of 42 notifications of nosocomial transmission events (three in 2008, 10 in 2009 and 29 since January 2010). Among the notified events, 30 involved at least one HCW, and 44 of 61 cases (72%) were HCWs. Two of the three nosocomial transmission events in 2008 occurred in spite of a low prevalence of measles susceptibility in HCWs [4-7].

We agree with Botelho-Nevers *et al.* that due to the high contagiousness of measles, its control in healthcare settings can not rely only on barrier measures and that all efforts should be made to ensure that HCW are properly immunised. According to national recommendations, HCWs born in 1980 or later are targeted by the general catch-up immunisation strategy which consists in a single dose of measles-containing vaccine for all adults, HCW or not [8].

A control of measles serology among HCWs (in position as well as students or applicants) born before 1980 without a reliable history of measles or vaccination is recommended and vaccination should be proposed in case of a negative result. Mandatory measles serology for hospital staff would certainly increase the knowledge of HCWs of their immune status for measles. However recruiting only immunised HCWs for at-risk medical wards would be very difficult to implement in the current context of staff shortage, and quite impossible for medical students.

Our data confirm the insufficient implementation of current recommendations issued by the French health authorities and therefore the difficulty in preventing measles in healthcare settings. However, this difficulty is partly offset by the recommendation,to administrate immediately after a contact with a confirmed measles case one dose of measles-mumps-rubella (MMR) vaccine to HCWs who were not previously vaccinated with two doses of MMR vaccine or who can not provide a serological proof of immunity.

It would be helpful to identify the reason behind the low compliance of healthcare professionals regarding the knowledge of their serological status and/or the updating of their vaccination status. Ongoing efforts to sensitize HCWs regarding the risk of transmission from pre-symptomatic contagious HCWs measles cases to severe measles at-risk patients (e.g. immunocompromized patients) should be maintained.

References

1. Parent du Châtelet I, Antona D, Freymuth F, Muscat M, Halftermeyer-Zhou F, Maine C et al. Spotlight on measles 2010: Update on the ongoing measles outbreak in France, 2008-2010. Euro Surveill. 2010;15(36):pii=19656. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19656
2. Botelho-Nevers E, Chevereau L, Brouqui P. Letter. Spotlight on measles 2010: Measles in healthcare workers – vaccination should be revisited. Euro Surveill. 2010;15(41):pii=19687. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19687
3. The RAISIN Working Group. "RAISIN" – a national programme for early warning, investigation and surveillance of healthcare-associated infection in France. Euro Surveill. 2009;14(46):pii=19408. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19408
4. Sillam F, Cua E, Faudeux D, Peloux-Petiot F, Negre A, Six C, et al. Investigation d'une épidémie de rougeole avec transmissions nosocomiales en région Provence-Alpes-Côte d'Azur et dans la Principauté de Monaco, mars - mai 2008. Quels enseignements en tirer? [Investigation of a measles outbreak with nosocomial transmission in Provence-Alpes-Côte d'Azur and in the Principality of Monaco, March-May 2008. What are the lessons learned?]. [French.] Bull Epidemiol Heb. 2009;39-40:424-6. Available from: http://www.invs.sante.fr/beh/2009/39_40/beh_39_40_2009.pdf
5. Bureau-Chalot A, Brodard V, Oud N, Touche S, Bajolet O, Abely M, et al. [Gestion d'une épidémie hospitalo-communautaire de rougeole au CHU de Reims, janvier-mars 2008. [Management of a hospital/community measles outbreak at the Reims University Hospital, January-March 2008]. [French]. Bull Epidemiol Heb. 2009;39-40:427-9. Available from http://www.invs.sante.fr/beh/2009/39_40/beh_39_40_2009.pdf
6. Thierry S, Alsibai S, Parent du Chatelet I, on behalf of the investigation team. An outbreak of measles in Reims, eastern France, January-March 2008--a preliminary report. Euro Surveill. 2008;13(13):pii=8078. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8078

7. Touche S, Delavelle AC, Lundu B, Brodard V, Lévêque N. Rougeole au CHU de Reims en 2008 : statut immunitaire des soignants. [Measles in a teaching hospital in Reims, France, in 2008: immune status of health care workers]. [French]. Bull Epidemiol Heb. 2009;39-40:430-2. Available from http://www.invs.sante.fr/beh/2009/39_40/beh_39_40_2009.pdf
8. French Ministry of Health and Sports. CIRCULAIRE N°DGS/RI1/2009/334 du 4 novembre 2009 relative à la transmission obligatoire de données individuelles à l'autorité sanitaire en cas de rougeole et la mise en oeuvre de mesures préventives autour d'un cas ou de cas groupés. [Circular No. DGS/RI1/2009/334 of 4 November 2009 on the mandatory notification of individual data to the health authority in case of measles and implementation of preventive measures around a case or a cluster]. [French]. Available from: http://www.sante-sports.gouv.fr/IMG/pdf/09_334topdf.pdf

Letter to the editor. Spotlight on measles 2010: Timely administration of the first dose of measles vaccine in the context of an ongoing measles outbreak in France

A Gagneur (arnaud.gagneur@usherbrooke.ca)[1], D Pinquier[2]
1. Université de Sherbrooke, CHUS Fleurimont, Département de Pédiatrie. Sherbrooke, Québec, Canada
2. Hôpital Charles Nicolle, Pôle Mère-Femme-Enfant, Centre Hospitalier Universitaire Rouen, France

Citation style for this article:
Gagneur A, Pinquier D. Letter to the editor. Spotlight on measles 2010: Timely administration of the first dose of measles vaccine in the context of an ongoing measles outbreak in France. Euro Surveill. 2010;15(41):pii=19689. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19689

Article published on 14 October 2010

To the editor: Parent du Châtelet *et al.* recently described the ongoing measles outbreak in France [1]. We would like to highlight a specific aspect of this outbreak: the significant change in the age distribution of measles cases. In fact, the proportion of cases aged under one year has increased significantly from 2008 to 2010 and this population represents to date the highest incidence rate [1]. Several factors could explain this phenomenon, leading to the question of the necessity of specific control measures in response to the increase of measles cases in the under one year-olds.

During the first year of life, protection against measles is conferred by transferred maternal antibodies. Since the introduction of the measles vaccine, changes in epidemiology have had major effects on the transmission of protective antibodies. The majority of women of childbearing age are now vaccinated and transfer fewer antibodies than naturally immune mothers, conferring protection over a shorter period of time than before to their offspring [2]. A recent French study confirms this fact, showing first that measles antibodies titres were significantly lower in women born after the implementation of the vaccine [2] and secondly that at six months of age, 90% of infants were not protected whatever the mothers' immunisation status (vaccinated or naturally immune) [3]. Several studies confirm this fact, notably Leuridan *et al.* demonstrating a median presence of maternal measles antibodies of 3.78 months for infants of naturally immune mothers and 0.97 for infants of vaccinated mothers [4]. Furthermore, the decrease in antibody levels in women of childbearing age may be amplified by three phenomena: first, childbearing age is increasing, with an increased interval between childhood vaccination in the mother and childbirth, resulting in a diminution in antibody levels; and second, boosting by wild type viruses occurs less often as vaccination coverage increases, and this may contribute further to lowering antibody levels in both vaccinated and naturally immune women. In addition, an increasing number of unprotected mothers is being observed, due to failure in catch-up strategies [3].

The result of this early loss of maternal antibodies is the apparition of a critical window of risk for measles infection during the first year of life, which should give rise to several modifications of the measles vaccination programme. One of the barriers to earlier vaccination is the presumed immaturity of the neonatal immunological system. However several studies demonstrate both humoral and cellular responses at an early age [4]. For example, Gans *et al.* demonstrated priming of infant T-cells with measles antigen as early as six months of age, despite the presence of maternal antibodies [5].

In France, recommendations have been made for vaccination at 12 months of age, and a second dose during the second year of life. Specific recommendations have been made for vaccination at nine months of age for infants in day care centres, with a second dose between 12 to 15 months. In case of contact between infants aged six to eight months and people with measles, vaccination with monovalent vaccine is recommended within 72 hours after contact [3]. Considering that the highest age-specific incidence rate is found in children under one year [1], demonstrating early loss of maternal antibodies, policy makers could consider advancing the measles vaccination programme to, for example, nine months for all infants. In fact, these infants need direct protection until the catch-up vaccination programme can reduce the susceptible population as well as disease transmission.

Early loss of maternal measles antibodies is well documented to date [2-4]. The high number of measles cases in the population under one year of age illustrates this fact. This underscores the importance of timely administration of the first dose of measles vaccine in the context of the ongoing measles outbreak in France and Europe.

References

1. Parent du Châtelet I, Antona D, Freymuth F, Muscat M, Halftermeyer-Zhou F, Maine C et al. Spotlight on measles 2010: Update on the ongoing measles outbreak in France, 2008-2010.

Euro Surveill. 2010;15(36):pii=19656. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19656

2. Pinquier D, Gagneur A, Aubert M, Brissaud O, Le Guen CG, Hau-Rainsard et al. Distribution of serum measles-neutralizing antibodies according to age in women of childbearing age in France in 2005-2006: impact of routine immunization. Pediatr Infect Dis J. 2007;26(8):749-50.
3. Gagneur A, Pinquier D, Aubert M, Soubeyrand B, Balu L, Brissaud O et al. Kinetics of decline of maternal measles virus-neutralizing antibodies in sera of infants in France in 2006. Clin Vaccine Immunol. 2008;15(12):1845-50.
4. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ. 2010;18;340:c1626.
5. Gans HA, Yasukawa LL, Alderson A, Rinki M, DeHovitz R, Beeler J et al. Humoral and cell-mediated immune responses to an early 2-dose measles vaccination regimen in the United States. J Infect Dis. 2004;190(1):83-90.

Authors' reply. Spotlight on measles 2010: Timely administration of the first dose of measles vaccine in the context of measles outbreak in France

D Floret (daniel.floret@chu-lyon.fr)[1]
1. Claude Bernard Lyon 1 University, French working group on measles and congenital rubella elimination, Lyon, France

Citation style for this article:
Floret D. Authors' reply. Spotlight on measles 2010: Timely administration of the first dose of measles vaccine in the context of measles outbreak in France. Euro Surveill. 2010;15(41):pii=19686. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19686

Article published on 14 October 2010

To the editor: We thank Gagneur and Pinquier for their interest to the paper [1] and share their concern with respect to the high incidence of measles in children under one year of age, as observed in the ongoing measles epidemics in France.

General immunisation at the age of nine months has been discussed in 2005 when the immunisation schedule has been modified in the context of the implementation of the French National Plan for elimination of measles and congenital rubella [2]. At that time, this was considered not relevant because the majority of childbearing women had acquired immunity through natural infection and would thus transfer to their newborn a high level of antibodies able to inhibit living vaccine measles virus for a long time. We agree with Gagneur and Pinquier that the situation has changed and that at present, the majority of childbearing women, born in 1983 or later, have acquired immunity through vaccination, which results in more rapidly waning antibody levels in the newborns. In theory, administration of measles-mumps-rubella (MMR) vaccine at nine month of age seems now possible.

However, in the opinion of doctors who provide vaccination, repeated modifications of immunisation schedules appear worrisome. Measles vaccine was recommended for children in France in 1983 and changed to one dose of MMR vaccine in 1986. A second dose at the age of 11-13 years was recommended in 1993, then at the age of 3-6 years in 1997. In 2005, the immunisation schedule was again changed with the first dose at one year of age and the second dose during the second year of life. Other modifications in the general immunisation schedule of young children might be considered in the near future. It would probably be more convenient to reconsider the age of first administration of MMR vaccine at that time. Furthermore, our immunisation schedule is somewhat crowed in the first year of life and could become more so if new vaccines (such as meningococcal B vaccines) are introduced.

As stressed by Gagneur and Pinquier, some studies [3] have demonstrated the existence of both a humoral and cellular immune response to measles vaccine when administrated early in life, even in the presence of maternal antibodies. "However, since a modification of the summary of product characteristics (SPC) of the M-M-R-VAXPRO vaccine was needed to allow its administration at nine months of age, the immune response according to the age of administration has been studied [4]: after the second dose (administered three months after the first), children who had received the first dose at nine months of age had a seroprotection rate against measles of 94.6%, (95% confidence interval (CI): 92.3–96.4) compared to 98.9% (95% CI: 97.5–99.6) for those vaccinated at 12 months of age. Similarly, geometric mean antibodies titres for measles was significantly lower in children immunised at age nine months. So, the SPC mentions that administration of this vaccine at nine months of age should be reserved to certain circumstances (for example for children admitted to day-care centres, for epidemics and for travel in countries with high incidence of measles) and that an additional dose (i.e. a third dose) of vaccine should be provided to children who received the first dose at nine months of age [4].

In our study 135 (56%) of the notified cases in children aged under one year were under nine months-old. Thus, starting the immunisation at nine months of age would have left the majority of them unprotected.

Finally, we know that the current prolonged outbreak of measles in our country is due to the existence of a large cohort of susceptible children, adolescents and young adults who had neither the vaccination nor the disease. In our opinion, reducing the size of this cohort by catch-up vaccination campaigns in the unvaccinated population (according to the official recommendations) is the best way to interrupt the circulation of measles virus and to protect the infants through herd immunity.

References

1. Gagneur A, Pinquier D. Letter. Spotlight on measles 2010: Timely administration of the first dose of measles vaccine in the context of measles outbreak in France. Euro Surveill. 2010;15(41):pii=19689. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19689
2. Plan d'élimination de la rougeole et de la rubéole congénitale en France 2005-2010. [Elimination plan for measles and congenital rubella in France 2005-2010]. [French]. Paris: Ministère de la Santé et desSolidarités; June 2005. Available from: http://www.sante.gouv.fr/htm/dossiers/rougeole/plan_national.htm
3. Gans HA, Yasukawa LL, Alderson A, Rinki M, Dehovitz R, Beeler J, et al. Humoral and cell-mediated immune response to an early 2-doses measles vaccination regimen in the United States. J Infect Dis. 2004;190(1):83-90.
4. M-M-RVAXPRO. Summary of product characteristics. Updated 25 May 2010. Available from: http://ec.europa.eu/health/documents/community-register/2010/2010090688568/anx_88568_en.pdf