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

Vol. 16 | Weekly issue 22 | 02 June 2011

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Update on the ongoing outbreak of haemolytic uraemic syndrome due to Shiga toxin-producing *Escherichia coli* (STEC) serotype O104, Germany, May 2011

M Askar (AskarM@rki.de)[1,2,3], M S Faber[1], C Frank[1], H Bernard[1], A Gilsdorf[1], A Fruth[4], R Prager[4], M Höhle[1], T Suess[1], M Wadl[1], G Krause[1], K Stark[1], D Werber[1]

1. Robert Koch Institute, Berlin, Germany
2. Postgraduate Training for Applied Epidemiology (PAE, German Field Epidemiology Training Programme), Robert Koch Institute, Department for Infectious Disease Epidemiology, Berlin, Germany
3. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
4. National Reference Centre for Salmonella and other Bacterial Enteric Pathogens, Robert Koch Institute, Wernigerode, Germany

Citation style for this article:
Askar M, Faber MS, Frank C, Bernard H, Gilsdorf A, Fruth A, Prager R, Höhle M, Suess T, Wadl M, Krause G, Stark K, Werber D. Update on the ongoing outbreak of haemolytic uraemic syndrome due to Shiga toxin-producing Escherichia coli (STEC) serotype O104, Germany, May 2011.
Euro Surveill. 2011;16(22):pii=19883. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19883

Article published on 2 June 2011

Since early May 2011, a large outbreak of haemolytic uraemic syndrome (HUS) and bloody diarrhoea related to infections with Shiga toxin-producing Escherichia coli (STEC) has been observed in Germany. The outbreak is focused in the north, but cases have been reported from all German states and other countries. Since our report last week, the number of HUS cases has increased to 470 and STEC serotype O104 has been confirmed in many cases.

Description of the ongoing outbreak

Since the beginning of May 2011, 470 cases of haemolytic uraemic syndrome HUS have been notified to the Robert Koch Institute (RKI). Our initial findings have been presented [1], including background information on STEC infections and HUS. The clinical and laboratory case definitions used are available [2]. Here we give an update on the epidemiological characteristics of the outbreak concerning cases of STEC and HUS notified to the Robert Koch Institute as of 31 May 2011.

Of 470 HUS cases, 273 (58%) were clinical cases with laboratory confirmation of Shiga toxin-producing *Escherichia coli* (STEC) infection. The German National Reference Centre for Salmonella and other Bacterial Enteric Pathogens alone has detected STEC serotype O104, Shiga toxin 2 (*stx2*)-positive, intimin (*eae*)-negative in more than 60 samples from cases in the outbreak, indicating that this unusual serotype is the cause of the outbreak.

Geographical distribution of HUS cases

Cases of HUS have been notified from all German Federal states. The highest cumulative incidence of HUS, since 1 May 2011, continues to be observed in the five northern states: Hamburg, Schleswig-Holstein, Bremen, Mecklenburg-Vorpommern and Lower Saxony (Table). A total of 66% of HUS cases have been notified from these states.

Epidemiological development

From 1 to 8 May 2011, the number of new HUS cases was between one and two cases per day, based on the

Table

Notified cases and cumulative incidence of HUS since 1 May 2011, Germany (n=470)

Federal State	Number of HUS cases	Cumulative incidence (per 100,000 population)
Hamburg	97	5.47
Schleswig-Holstein	121	4.27
Bremen	22	3.32
Mecklenburg-Vorpommern	20	1.21
Lower Saxony	51	0.64
Hesse	33	0.54
Saarland	5	0.49
North Rhine-Westphalia	75	0.42
Berlin	9	0.26
Saxony-Anhalt	4	0.17
Thuringia	3	0.13
Baden-Württemberg	13	0.12
Brandenburg	3	0.12
Rhineland-Palatinate	4	0.10
Bavaria	9	0.07
Saxony	1	0.02
Total	**470**	**0.57**

HUS: haemolytic uraemic syndrome.
Data as of 31 May 2011, 3 pm.

date of onset of diarrhoea (Figure 1). From 9 May, we observed an initially steady increase in the number of cases. This increase gained in intensity over the following days and reached a maximum of 39 notified HUS cases on 16 May.

Age and sex distribution of HUS cases

As reported on 26 May 2011 [1], the age and sex distribution of HUS cases remain conspicuous: the majority of patients were aged 20 years or older (88%) and female (71%). Notably, between 2006 and 2010, the proportion of adults in reported STEC and HUS cases was only between 1.5% and 10%, and there were no marked differences in sex distribution [3]. Figure 2 shows the age- and sex-specific cumulative incidence of notified cases of HUS since 1 May 2011.

Fatal cases

To date, 13 deaths have been notified: in nine cases, the deaths were in connection with HUS; in the remainder, the cases had had symptomatic STEC infection that was laboratory confirmed. The cases who died were between 22 and 91 years of age: five were aged between 22 and 40 years and eight between 75 and 91 years of age.

Foreign cases with connection to the present outbreak

Further HUS cases have been communicated from Denmark, United Kingdom, France, Netherlands, Norway, Austria, Spain, Sweden (including one death), Switzerland and the United States. Nearly all of these cases had a travel history to northern Germany. For some cases, however, detailed investigations are ongoing. After a stay in northern Germany between 8 and 10 May 2011, 15 members of a Swedish travel group (30 members in total) developed symptoms of STEC infection and HUS was diagnosed in five of these cases.

Evaluation of the situation

The present situation marks one of the largest outbreaks ever described of HUS worldwide, and the largest outbreak ever reported in Germany. Because of the delay in notification and reporting of cases, the current notification data cannot be interpreted as a decrease in case numbers.

The age and sex distribution of cases in this outbreak is highly unusual, as is the identified outbreak strain: STEC O104, Shiga toxin 2 (*stx2*)-positive, intimin (*eae*)-negative. Serotype STEC O104 has caused food-borne outbreaks of diarrhoea and HUS, or isolated cases of HUS before [4,5], but is not known to have caused previous outbreaks in Germany.

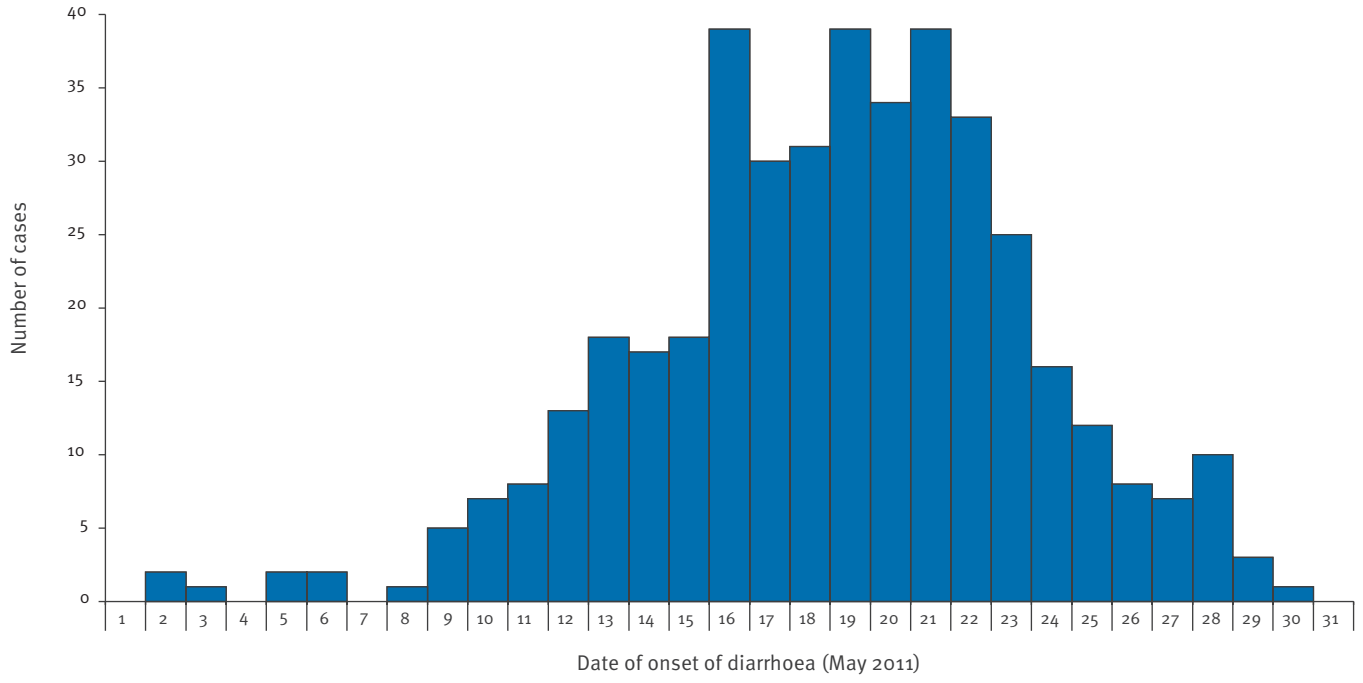
Current epidemiological activities

RKI is currently conducting the following studies to further investigate the outbreak:

- representative online survey within the German population to describe the disease burden;

Figure 1

Notified cases of HUS by date of onset of diarrhoea (only cases with a notified date of onset since 1 May 2011), Germany (n=421)



HUS: haemolytic uraemic syndrome.
Data as of 31 May 2011, 3 pm.

- case–control study in heavily affected hospitals, in Lübeck (in Schleswig-Holstein) and Hamburg;
- case–control study in hospitals that have observed a recent increase in cases numbers and had not been previously affected;
- analyses of questionnaires on cases completed by nephrologists treating the cases;
- Investigation of human-to-human transmission (and of information about purchases made by analysis of till receipts) within the setting of a special outbreak in a canteen;
- cohort investigations of various groups, in which several members developed symptoms of STEC infection after dinner in a restaurant (the members of the groups are questioned about the food products they consumed);
- exploration of several events and festivities that can be related to cases.

Furthermore, the RKI is cooperating with colleagues from Sweden and Denmark, who are performing cohort studies of groups in which several members developed symptoms of STEC infection.

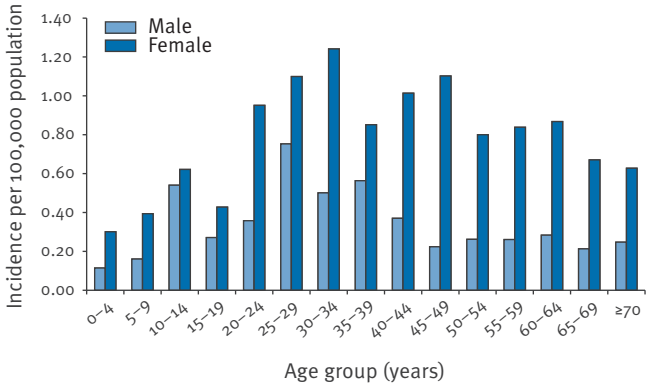
The Federal Institute for Risk Assessment (BfR) has recommended that consumers in Germany abstain from eating raw tomatoes, cucumbers and leafy salads (based on results from an epidemiological study, conducted by the RKI in cooperation with regional and local health departments from Hamburg [1]). As long as the studies outlined above do not lead to new evidence and as long as the outbreak is still ongoing, these recommendations – concerning goods available in northern Germany in particular – remain in effect.

Acknowledgments

We gratefully acknowledge the contribution of all local and state health departments, whose investigations and notifications were the data basis of this report, as well as the contribution of the health authorities of other European countries affected by the outbreak.

Figure 2

Cumulative incidence of HUS cases notified since 1 May 2011, by age and sex, Germany (n=470)



HUS: haemolytic uraemic syndrome.
Data as of 31 May 2011, 3 pm.

References

1. Frank C, Faber MS, Askar M, Bernard H, Fruth A, Gilsdorf A, et al. Large and ongoing outbreak of haemolytic uraemic syndrome, Germany, May 2011. Euro Surveill. 2011;16(21):pii=19878. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19878
2. Robert Koch Institute (RKI). Case definition for HUS-cases associated with the outbreak in the spring 2011 in Germany. HUS-Outbreak_Case-Definition_2011-06-01_ENG.doc . Available from: http://www.rki.de/cln_116/nn_217400/EN/Home/HUS__Case__definition,templateId=raw,property=publicationFile.pdf/HUS_Case_definition.pdf
3. Robert Koch Institute (RKI). SurvStat@RKI. Berlin:.RKI. [Accessed 24 May 2011]. German. Available from: http://www3.rki.de/SurvStat
4. Bea WK, Lee YK. Cho MS, Ma SK, Kim SW, Kim NH, et al. A case of hemolytic uremic syndrome caused by Escherichia coli 104:H4.
   Yonsei Med J. 2006;47(3):437-9.
5. Centers for Disease Control and Prevention (CDC). Outbreak of acute gastroenteritis attributable to Escherichia coli serotype O104:H21--Helena, Montana, 1994. MMWR Morb Mortal Wkly Rep. 1995;44(27):501-3.

Hepatitis B prevention in Victoria, Australia – the potential to protect

S Williams (stephanie.williams@health.vic.gov.au)[1,2,3], H Vally[2,4], J Fielding[1,3], B Cowie[3,5]
1. Communicable Disease Prevention and Control Unit, Department of Health, Victoria, Australia
2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia
3. Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia
4. School of Public Health, La Trobe University, Melbourne, Australia
5. Victorian Infectious Diseases Service, The Royal Melbourne Hospital and Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Australia

Citation style for this article:
Williams S, Vally H, Fielding J, Cowie B. Hepatitis B prevention in Victoria, Australia – the potential to protect.
Euro Surveill. 2011;16(22):pii=19879. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19879

Article published on 2 June 2011

People with chronic hepatitis B (CHB) are a major source of incident hepatitis B virus (HBV) infection. The Department of Health in Victoria, Australia, recommends household contacts of CHB cases to be screened and funds hepatitis B vaccination for those susceptible to infection. In July 2009, two cross-sectional surveys were conducted to assess the uptake of screening and vaccination: a postal survey of the treating doctors of a random sample of 65 CHB patients and a telephone survey of these patients. Twenty-six cases reported all adult household contacts had been screened, however only eight of these 26 patients reported that all susceptible adult contacts had been fully vaccinated. In contrast, child contacts of only three cases had been screened but 15 reported all child contacts to be fully vaccinated. Half of the surveyed doctors were unaware of state-funded hepatitis B vaccine for contacts and only 10 had conducted any contact tracing. This study highlights the need for health departments to play a greater role in the management of CHB patients in order to support doctors' delivery of preventive services to people at high risk of HBV infection. These findings are relevant for all countries receiving immigrants from areas where hepatitis B is endemic.

Introduction

Worldwide, about $2x10^9$ people have been infected with the hepatitis B virus (HBV), and more than 350 million live with chronic hepatitis B (CHB) virus infection [1]. Estimates of mortality attributable to CHB range from 600,000 to over 1 million deaths annually [1-3]. Australia is a low-prevalence country, with a hepatitis B surface antigen (HBsAg) prevalence of less than 2% [4-6]. Over the last 20 years, however, the prevalence of CHB has increased, predominantly related to the increase in migration from highly endemic regions [7,8]. Currently there are an estimated 165,000 people with CHB infection in Australia, more than half of whom were born in other countries of the Asia-Pacific region [7-9]. About 55,000 of those infected are unaware of their diagnosis [10,11]. Predominant risk factors for CHB in Australia are birth in a high prevalence country or being an Aboriginal or Torres Strait Islander [7].

In Australia, hepatitis B infections are reported as acute or unspecified (non-acute). Unspecified hepatitis B (herein referred to as CHB) requires detection of HBsAg, or HBV by nucleic acid testing, in a patient with no prior evidence of HBV who does not meet criteria for acute infection [12.] In Victoria, from 1998 to 2008, there were a total of 19,024 cases of confirmed CHB reported through the notifiable disease surveillance system, with between 1,497 and 1,938 cases annually [13]. Notification rates for CHB in the Melbourne metropolitan region were significantly higher than in non-metropolitan regions of Victoria, reflecting findings of a recent serosurvey [14].

CHB is associated with significant morbidity and mortality. Approximately 25% of people with CHB develop advanced liver disease including cirrhosis and/or hepatocellular carcinoma (HCC) [3,15]. This excess mortality was demonstrated in a recent data linkage study in New South Wales, Australia that found that people living with CHB had standardised all-cause mortality 1.4 times higher than those without CHB [10]. In New South Wales, HCC incidence is rising faster than any other internal cancer [16,17].

In Australia, universal hepatitis B vaccination for adolescents commenced in 1998 and for infants in 2000, with the first of four doses given at birth [9]. In Victoria, in addition to the national immunisation programme, hepatitis B vaccination is funded for healthcare workers, people who inject drugs, and household or sexual contacts of patients with CHB and people living with human immunodeficiency virus or acquired immunodeficiency syndrome (HIV/AIDS) [18]. Serologic testing before vaccination is recommended for families of CHB patients, as well as for members of families who have migrated from high-prevalence countries [5].

Chronically infected individuals are a source of incident infections (in low and high prevalence countries alike) [19-22]. Furthermore, persons with undiagnosed CHB can remain asymptomatic for years and unaware of their risk for transmitting the virus to others or having liver disease in later life [21,23]. Therefore an adequate public health response to incident HBV infections must reduce opportunities for transmission from those chronically infected to those who are susceptible [21,22].

Currently it is unknown whether or not tracing the household contacts of CHB patients takes place in accordance with Victorian recommendations, and the uptake of the funded hepatitis B vaccine for contacts of CHB patients has not been evaluated. Consequently, the objectives of this study were firstly, to ascertain the uptake of screening and vaccination in household contacts of patients with CHB, and secondly, to explore barriers to vaccination amongst household contacts of CHB cases.

Methods

Study population

Patients were randomly selected from the Notifiable Infectious Diseases Surveillance database maintained by the Victorian Department of Health. Patients were eligible for the study if they were notified to the department with CHB between 1 July 2008 and 31 December 2008 (n=989). Our target sample size was 65 patients. Patients were excluded if no notifier details were recorded, or if no contact details for the cases were available after checking with the notifying doctor and/or laboratory.

Study design

In Victoria, if a patient is randomly selected from the surveillance database as part of a study, it is customary that treating doctors are contacted first to ensure the patient is aware of their diagnosis prior to inviting their participation. We conducted two cross-sectional surveys to gather information from doctors and patients about patients and their household contacts.

The first survey was a postal survey sent to the doctors of 65 patients randomly selected from the 989 CHB patients. The second was a telephone survey of those patients whose treating doctor had given consent for the investigators to contact their patient. On calling patients, a confidentiality statement was read to each patient, verbal consent obtained and an appointment was made to interview them.

The doctor survey assessed knowledge of the Victorian recommendations regarding the hepatitis B vaccine and attitudes about a doctor's role in contact tracing. It also assessed whether the doctors had attempted to trace household contacts of their patient in the sample, and if so, whether they documented the screening and vaccination status of their patients' household contacts.

The patient survey assessed the uptake of screening and vaccination of household contacts following the index patient's diagnosis. Interviews were conducted with an interpreter when necessary. The principal outcome was the proportion of patients whose susceptible household contacts had been fully vaccinated against hepatitis B. Patients were asked for each contact's age, screening history, and if susceptible to HBV, the number of doses of hepatitis B vaccine received. Vaccination of contacts and serologic confirmation of immunity were reported by the patients and not otherwise verified, and reasons for non-vaccination were sought when applicable.

A secondary aim of the patient survey was to assess knowledge regarding hepatitis B transmission by asking respondents to provide an example of how to prevent the spread of hepatitis B infection. Patients were considered to have an understanding of preventing spread if they stated any one of the following methods: no sharing of certain household items such as razors, keeping wounds covered, practising safe sex, no donation of blood or organs, or vaccination of contacts.

Data analysis

Data were entered into Microsoft Access and analyses conducted using STATA v9. Household contacts' vaccination status was analysed according to each patient because household contact observations are not independent. If all adult and/or child contacts of a patient had been tested or vaccinated, this was considered a positive outcome. If a patient was uncertain about the status of any contact, all contacts of that patient were excluded from the analysis.

Ethics

Human research ethics approval was granted by The Australian National University (Study number 2009/552).

Results

The surveys were conducted in June and July 2009. Twenty-four doctors returned the surveys and two doctors were interviewed by telephone for a doctor response rate of 26 of 65. We telephoned the 39 doctors who had not responded to the postal survey and obtained consent from 21 of them to call their patient. Therefore a total of 47 patients were eligible. Of these, four patients were unable to be contacted and doctors of five patients requested their patient not be contacted by the investigators. The remaining 38 patients all agreed to participate in the study.

Doctor survey

The majority of doctors who participated in the study were metropolitan general practitioners (GPs) (23/26). Others included two hospital-based doctors and one rural GP. Of 39 non-responders, 37 were metropolitan GPs and the remaining two represented private blood screening services. As our sampling frame was CHB patients, doctors that did and did not participate in our study reflect

that CHB notifications are concentrated in metropolitan regions and largely managed in primary care settings.

Thirteen of 26 doctors were aware that hepatitis B vaccine for household contacts of CHB cases was funded by the Victorian Department of Health. All doctors agreed that general practitioners have a role in contact tracing for hepatitis B, however only 10 indicated that they had attempted contact tracing for their patient. Nine doctors suggested reasons for non-uptake of vaccination in household contacts: language and cultural barriers (n=3), the perceived impact of having hepatitis B on Australian residency applications (n=2), and difficulty systematically following up contacts (n=4).

Patient survey

The study population consisted of 47 patients of which 24 were male and 23 were female. The median age at notification for all patients was 34 years (interquartile range (IQR) 27–44 years).(Table 1). Forty-four patients lived in metropolitan Melbourne. Seven patients were interviewed with an interpreter.

Table 1

Patient demographics, hepatitis B patients, Victoria, 1 July–31 December 2008 (n=47)

		Number	Percentage
Sex			
	Male	24	51%
	Female	23	49%
	Total	**47**	**100%**
Age (years)			
	10–17	1	2%
	18–29	16	34%
	30–49	22	47%
	50–69	6	13%
	70–89	2	4%
	Total	**47**	**100%**
Region of residence			
	Metropolitan	44	94%
	Rural	3	6%
	Total	**47**	**100%**
Country of birth			
	Australia	3	6%
	Overseas	44	94%
	Total	**47**	**100%**
Years of arrival[a]			
	1950–1959	2	5%
	1960–1969	1	3%
	1980–1989	4	10%
	1990–1999	6	15%
	2000–2008	26	67%
	Total	**39**	**100%**

[a] For whom this information as known.

Forty-four patients were born overseas. Approximately half of them were born in Vietnam (n=12) and China (n=11) (Table 2). Information on the year of their arrival in Australia was available for 39 of these patients and ranged from 1958 to 2008. More than two thirds of the 39 patients (n=26) had arrived since 2000. For patients born overseas, the median time between arrival in Australia and notification with CHB was five years (IQR 1–17 years).

Of 38 patients interviewed, 18 had been aware of their hepatitis B infection up to several years prior to notification in 2008. Eleven of these 18 patients had been tested in their country of birth prior to arrival in Australia. For patients diagnosed in their country of birth, the median time between first diagnosis and notification in Australia was 8.5 years (IQR 2.5–11 years).

Of the 32 patients who answered the question about transmission of hepatitis B, the most common responses were avoiding unprotected sex (n=8) or avoiding blood donation (n=7). Thirteen patients were unable to give an example of how to prevent the spread of the virus. Two patients said that not sharing cups and spoons prevented the spread and one patient believed the virus was transmitted by food. Only one patient suggested vaccination of family members prevented the transmission of the virus.

Household contact vaccination results

Household contact information was available for 41 patients. Patients commonly had one adult household contact (n=19) and no contacts under the age of 18

Table 2

Countries of birth, hepatitis B patients, Victoria, 1 July–31 December 2008 (n=44)

Countries of birth	Number	Percentage
Vietnam	12	27%
China	11	25%
New Zealand	3	7%
Burma	3	7%
Sudan	2	5%
Cambodia	2	5%
Thailand	2	5%
Afghanistan	1	2%
India	1	2%
Greece	1	2%
Romania	1	2%
Italy	1	2%
Liberia	1	2%
Bangladesh	1	2%
Kuwait	1	2%
Netherlands	1	2%
Total	**44**	**100%**

(n=17). For 37 of these 41 patients, household contacts included family members only.

Twenty-six patients reported that all adult household contacts had been tested for hepatitis B. Testing histories of all child contacts were available for 21 patients and of these, only three cases reported all eligible child contacts had been tested (Table 3). Children were considered eligible for testing if they were older than 18 months of age.

Information about vaccination of all eligible adult contacts was available for 26 patients, and of all eligible child contacts, for 20 patients. Eligible adult contacts of 8 (31%, 95% confidence interval (CI): 12–50%) of 26 patients were reported to be fully vaccinated against hepatitis B. In contrast, the majority of patients with eligible child contacts (75%, 95% CI: 54–96%) reported that all had been fully vaccinated (Table 3). Child vaccination had occurred as part of the national immunisation programme in 11 patients, whereas the child contacts of four patients had been vaccinated as part of contact tracing despite being eligible for participation in the national immunisation programme (Table 3).

Barriers to screening and vaccination of contacts

Patients were asked for the reasons why any of their contacts were not vaccinated. Of 38 eligible adult contacts, responses were provided for 34 contacts of 22 patients. Most commonly, the patient reporting on the contact did not know the reason for non-vaccination (n=19) and least commonly the contact had refused vaccine (n=2). Four contacts were reported to be planning to start vaccination and 'other' reasons were stated for nine contacts. Only five patients expanded on 'other' reasons, which were fear of testing for hepatitis B, being unaware of the need for vaccination, living overseas, awaiting blood test results, and difficulty attending the GP.

Table 3

Testing and vaccination data of household contacts of hepatitis B patients, Victoria, 1 July–31 December 2008 (n=41 patients)

	Number	Percentage	95% CI
Patients for whom all adult contacts were screened			
Yes	26	68%	53-84%
No	12	32%	16-47%
Total	**38**	**100%**	
Patients for whom all eligible child contacts were screened			
Yes	3	14%	0-31%
No	18	86%	69-100%
Total	**21**	**100%**	
Patients whose adult contacts were all fully vaccinated			
Yes	8	31%	12-50%
No	18	69%	50-88%
Total	**26**	**100%**	
Patients whose child contacts were all fully vaccinated			
Yes	15	75%	54-96%
No	5	25%	4-46%
Total	**20**	**100%**	
Reason why children were vaccinated			
National immunisation programme	16	80%	61-99%
Contact tracing	4	20%	1-39%
Total	**20**	**100%**	

Discussion

Our study showed that, despite recommendations for contact tracing and funded hepatitis B vaccine, the adult household contacts of less than a third of CHB patients had been vaccinated against hepatitis B. In contrast, the child household contacts of 75% of patients were reported to be fully vaccinated, mostly attributable to universal vaccination. We found it concerning that only half of the surveyed doctors were aware that hepatitis B vaccine was funded for household contacts. This is likely to be a key provider barrier to vaccination of household contacts [24]. All surveyed doctors felt that GPs have a role to play in contact tracing, however only 37% had conducted any contact tracing for their notified patient. We inferred that this was due to lack of knowledge of funded vaccination policy and to the difficulty of organising contact management, especially if contacts were not patients of the doctor's practice. Currently the Victorian Health Department relies on doctors to manage the contact tracing, however our small study suggests this assumption may need revisiting. Doctors' efforts to provide preventive services to populations at high risk for infection may benefit from public health collaboration [20].

Although 26 of 38 patients reported their contacts had been screened for hepatitis B, only a small number had been vaccinated. This suggests that being tested (and reported to be susceptible) is not necessarily sufficient to ensure participation in vaccination. It is worrying that only eight of 26 patients reported that all their adult contacts had been fully vaccinated, but it is consistent with published findings from other countries: In the United States, a study in San Diego found less than 20% of eligible contacts (including children) had been vaccinated, and in the United Kingdom (UK), a similar study found only 27% of contacts had been vaccinated [20,25]. A 10-year seroprevalence review of hepatitis B in Italy also found 28% of new HBV cases were household contacts of CHB patients and had been unaware that free vaccine was available [26].

The limitations of this study included the small sample size of doctors and of patients that provided vaccination status of all of their contacts. In addition, obtaining a serological assessment of contacts' vaccination status would have strengthened the study, but this was not feasible. Previous studies have shown poor patient recall of their own vaccination status [27], therefore

it is be reasonable to assume that recall of contacts' vaccination would also be poor. However, this may not have affected parents' recall of the vaccination history of their children as much as their recall of the status of other adult contacts. Uncertainty was partially managed at the analysis stage by excluding patients who were unsure of the vaccination status of one or more of their contacts.

Despite the study limitations, we feel that the findings build the argument for increasing public health collaboration in the management of chronic hepatitis B. It is a challenge for public health practitioners to increase participation in preventive programmes among high risk groups, who are often the most difficult to reach [28,29]. However for CHB in Australia, this relies on individual private doctors to implement public health policies. There is evidence that high participation (>90%) of contacts in screening and vaccination can be achieved when integrated into current clinical models [30,31]. In Victoria, one intervention that could be introduced is direct communication of health information by mail or electronic mail between the health department and notified CHB patients. This aligns with the principles of the Ottawa Charter that communicating important health information is necessary to empower patients to manage their health [32], and could have the secondary benefit of improving the success of contact management [33]. Indeed, in a 2006 cohort study in the UK, receipt of written information about hepatitis B was positively associated with infants born to HBsAg-positive mothers completing hepatitis B vaccination [34].

This issue is not limited to Australia. In Europe there is geographical variation in the prevalence of HBV infection given the mixture of countries with medium and low HBsAg prevalence [22,35]. Furthermore, an increasing number of immigrants to Europe, often from highly endemic countries, is changing the hepatitis B epidemiology in low endemic countries [35]. In 2009, a survey of 25 European Union Member States plus Norway and Iceland revealed that 20 had universal hepatitis B vaccination programmes in addition to targeting specific risk groups, while seven countries maintained hepatitis B vaccine for risk groups only [36]. Close family contacts of CHB cases were included in the risk groups in 18 of the 20 countries with routine immunisation and in all seven countries with selective immunisation programmes. Only 10 of 17 countries reported that vaccine was free to all people at increased risk by lifestyle, which included household contacts [36]. The experience in Australia suggests that the implementation of these targeted vaccination policies may need evaluation.

In conclusion, the findings from our study suggest that the vaccination of adult household contacts of CHB patients is inadequate. Although child contacts born in Australia were more likely to be fully immunised, this was largely due to the national immunisation programme. Our findings suggest that barriers to contact tracing include a lack of patient knowledge regarding CHB, limited awareness on the part of doctors of the funded vaccine, and limited capacity of individual doctors to organise systematic follow up of patients' contacts. Although more information is needed about the uptake of, and barriers to, screening and vaccination of contacts of patients with CHB in Victoria, we believe that information from this study should inform policy and programme considerations. There is evidence that active contact tracing for CHB patients can result in high participation rates in at-risk populations and that contact tracing is not always integrated into the core business of general practice. Improved communication from the health department directly to CHB patients, better targeted screening, and integrated contact tracing programmes will be vital to tackling the growing burden of complications from CHB in Australia. These findings are relevant to other countries with high net migration from areas with medium to high HBsAg prevalence.

Acknowledgments

This study was completed when Stephanie Williams was a Master of Applied Epidemiology scholar at the Australian National University, funded by the Australian Government Department of Health and Ageing.

References

1. World Health Organization (WHO). Hepatitis B. Fact Sheet No.204. Geneva: WHO; August 2008. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/index.html
2. Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34(6):1329-39.
3. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97-107.
4. Wood N, Backhouse J, Gidding HF, Gilbert GL, Lum G, McIntyre PB. Estimates of chronic hepatitis B virus infection in the Northern Territory. Commun Dis Intell. 2005;29(3):289-90.
5. The Australian Immunisation Handbook. 9th ed. Canberra, Australia: Australian Government Department of Health and Ageing; 2008, updated 2009. Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home.
6. Clements CJ, Baoping Y, Crouch A, Hipgrave D, Mansoor O, Nelson CB, et al. Progress in the control of hepatitis B infection in the Western Pacific Region. Vaccine. 2006;24(12):1975-82.
7. O'Sullivan B, Gidding HF, Law M, Kaldor JM, Gilbert GL, Dore GJ, et al. Estimates of chronic hepatitis B virus infection in Australia, 2000. Aust N Z J Public Health. 2004;28(3):212-6.
8. Nguyen VT, Razali K, Amin J, Law MG, Dore GJ. Estimates and projections of hepatitis B-related hepatocellular carcinoma in Australia among people born in Asia-Pacific countries. J Gastroenterol Hepatol. 2008;23(6):922-9.
9. Gidding HF, Warlow M, MacIntyre CR, Backhouse J, Gilbert GL, Quinn HE, et al. The impact of a new universal infant and school-based adolescent hepatitis B vaccination program in Australia. Vaccine. 2007;25(51):8637-41.
10. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet. 2006;368(9539):938-45.
11. Cowie B, Kelly, H. Outcomes of a complex dynamic mathematical model of hepatitis B virus in Australia (PP-027). Proceedings of the 20th Conference of the Asian Pacific Association for the Study of the Liver (APASL); 2010 Mar 26-28; Beijing, China. Hepatol Int. 2010;4(1):101.

12. Australian national notifiable diseases and case definitions. Hepatitis B (unspecified) case definition. Canberra, Australia: Australian Government Department of Health and Ageing; Mar 2004. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hepbun.htm
13. Williams S, Vally H, Fielding J, Cowie B. Chronic hepatitis B surveillance in Victoria, 1998-2008: instituting a 21st century approach to an old disease. Aust N Z J Public Health. 2011;35(1):16-21.
14. Cowie B, Karapanagiotidis T, Enriquez A, Kelly, H. Markers of hepatitis B virus infection and immunity in Victoria, Australia, 1995 to 2005. Aust N Z J Public Health. 2010;34(1):72-8
15. Yuen MF. Revisiting the natural history of chronic hepatitis B: impact of new concepts on clinical management. J Gastroenterol Hepatol. 2007;22(7):973-6.
16. Robotin MC, George J, Supramaniam R, Sitas F, Penman AG. Preventing primary liver cancer: how well are we faring towards a national hepatitis B strategy? Med J Aust. 2008;188(6):363-5.
17. Coates M, Tracey E. Cancer in New South Wales: Incidence and mortality 1997. N S W Public Health Bull. 2001;12(2):40-2.
18. Immunisation Section. Criteria for government funded vaccine. Fact Sheet. Victoria, Australia: Victorian Government Department of Health; Nov 2010. Available from: http://www.health.vic.gov.au/__data/assets/pdf_file/0018/414171/Criteria-government-vaccine-Nov.10.pdf.
19. Hutton DW, Tan D, So SK, Brandeau ML. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. Ann Intern Med. 2007;147(7):460-9.
20. Weinberg MS, Gunn RA, Mast EE, Gresham L, Ginsberg M. Preventing transmission of hepatitis B virus from people with chronic infection. Am J Prev Med. 2001;20(4):272-6.
21. Weinbaum C, Williams I, Mast E, Wang S, Finelli L, Wasley A, et al. Recommendations for Identification and Public Health Management of persons with chronic hepatitis B. MMWR Recomm Rep. 2008;57(RR-8):1-20.
22. Rantala M, van de Laar MJ. Surveillance and epidemiology of hepatitis B and C in Europe - a review. Euro Surveill. 2008;13(21). pii:18880. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18880
23. Caruana SR, Kelly HA, De Silva SL, Chea L, Nuon S, Saykao P, et al. Knowledge about hepatitis and previous exposure to hepatitis viruses in immigrants and refugees from the Mekong Region. Aust N Z J Public Health. 2005;29(1):64-8.
24. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54(RR-16):1-31.
25. Richardson G, Evans M, Westmoreland D. Hepatitis B immunisation of household contacts: retrospective study of vaccine coverage. J Epidemiol Community Health. 2001;55(12):934-5.
26. Stroffolini T, Mele A, Tosti M, Gallo G, Balocchini E, Ragni P, et al. The impact of the hepatitis B mass immunisation campaign on the incidence and risk factors of acute hepatitis B in Italy. J Hepatol. 2000;33(6):980-5.
27. Tawk HM, Vickery K, Bisset L, Selby W, Cossart YE. The impact of hepatitis B vaccination in a Western country: recall of vaccination and serological status in Australian adults. Vaccine. 2006;24(8):1095-106.
28. Kretzschmar M, Mangen MJ, van de Laar M, de Wit A. Model based analysis of hepatitis B vaccination strategies in the Netherlands. Vaccine. 2009;27(8):1254-60.
29. van Houdt R, Koedijk FD, Bruisten SM, Coul EL, Heijnen ML, Waldhober Q, et al. Hepatitis B vaccination targeted at behavioural risk groups in the Netherlands: does it work? Vaccine. 2009;27(27):3530-5.
30. Williams SJ, Craig PI, Liddle C, Batey RG, Farrell GC. Hepatitis B in Australia: determinants of intrafamily spread. Aust N Z J Med. 1987;17(2):220-7.
31. van Steenbergen JE, Baayen D, Peerbooms PG, Coutinho RA, van den Hoek A. Much gained by integrating contact tracing and vaccination in the hepatitis B antenatal screening program in Amsterdam, 1992-1999. J Hepatol. 2004;40(6):979-85.
32. World Health Organization (WHO). Ottawa Charter for Health Promotion. First International Conference on Health Promotion: The move towards a new public health, Ottawa, Ontario, Canada. 17-21 Nov 1986. Geneva:WHO. Available from: http://www.who.int/hpr/NPH/docs/ottawa_charter_hp.pdf
33. Hahné S, Wörmann Nee Marschall T, Kretzschmar M. Migrants and hepatitis B: new strategies for secondary prevention needed. Eur J Public Health. 2009;19(4):439.
34. Giraudon I, Permalloo N, Nixon G, Charlett A, Cohuet S, Mandal S, et al. Factors associated with incomplete vaccination of babies at risk of perinatal hepatitis B transmission: a London study in 2006. Vaccine. 2009;27(14):2016-22.
35. Veldhuijzen I, Toy M, Hahné S, De Wit G, Schalm S, de Man RA, et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. Gastroenterology. 2010;138(2):522-30.
36. Mereckiene J, Cotter S, Lopalco P, D'Ancona F, Levy-Bruhl D, Giambi C, et al. Hepatitis B immunisation programmes in European Union, Norway and Iceland: where we were in 2009? Vaccine. 2010;28(28):4470-7.

Emergence of carbapenemase-producing Enterobacteriaceae in France, 2004 to 2011

S Vaux[1], A Carbonne[2], J M Thiolet[1], V Jarlier[3], B Coignard (b.coignard@invs.sante.fr)[1], RAISIN and Expert Laboratories Groups[4]
1. French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS), Saint-Maurice, France
2. Centre de coordination de la lutte contre les infections nosocomiales (CClin) Nord, Paris, France
3. Pierre et Marie Curie (Paris 6) University (EA1541), Paris, France
4. The participants of these groups are listed at the end of the article

Citation style for this article:
Vaux S, Carbonne A, Thiolet JM, Jarlier V, Coignard B, RAISIN and Expert Laboratories Groups. Emergence of carbapenemase-producing Enterobacteriaceae in France, 2004 to 2011.
Euro Surveill. 2011;16(22):pii=19880. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19880

Article published on 2 June 2011

Emergence of carbapenemase-producing Enterobacteriaceae (CPE) is currently a major public health concern worldwide. This study showed that 53 episodes of CPE infection or colonisation have been notified by French healthcare facilities since 2004. A sharp increase in the number of notifications was observed in the last three years. Oxacillinase (OXA)-48 and *Klebsiella pneumoniae* carbapenemase (KPC) beta-lactamases were the most frequent enzymes reported in these episodes. The index cases in most episodes were patients with a history of hospitalisation abroad within the previous year. Around a third of the episodes (n=18) led to secondary transmission in hospitals but most of them were controlled due to reinforced measures. Reinforcement of screening and control measures at national level when there is cross-border transfer of patients, along with overall reinforcement of infection control and antimicrobial stewardship worldwide, is urgently needed to contain the spread of CPE.

Introduction

As Enterobacteriaceae become increasingly resistant to antibiotics, carbapenems are among the few last-line drugs available for therapy against serious infections, such as pyelonephritis or bacteraemia, caused by multidrug-resistant strains, particularly those expressing extended-spectrum beta-lactamases. Resistance to carbapenems, resulting from carbapenemases, reduces the possibility of treating infections of multidrug-resistant strains. Carbapenemase-producing Enterobacteriaceae (CPE) have been reported increasingly worldwide and are becoming a major clinical and public health concern, as they constitute the last step towards a therapeutic dead end.

Carbapenemases belong to three molecular classes of beta-lactamases (A, B and D). Chromosome-encoded class A carbapenemases were first reported in 1994 [1]. The first plasmid-encoded class A carbapenemase, *Klebsiella pneumoniae* carbapenemase (KPC), was discovered in 1996 and reported for the first time in 2001 from the United States in a *K. pneumoniae* clinical isolate [2]. Since then, KPC-producing isolates have spread worldwide, notably in Greece and Israel, where they are now endemic [3,4]. The metallo-beta-lactamases (class B), such as Verona integron-encoded metallo-beta-lactamase (VIM) and imipenemase (IMP), are currently prevalent in Greece, Italy, Japan and Spain. Belonging to the same class, New Dehli metallo-beta-lactamase (NDM)-1 has recently emerged in India, Pakistan and the United Kingdom [5,6]. NDM-1 represents a serious threat of rapid dissemination of multiple antibiotic resistance since the majority of NDM 1-producing Enterobacteriaceae have been reported to remain susceptible only to colistin and tigecycline [5]. The first of the class D beta-lactamases with carbapenemase activity was described in 1995 [1]. Among this class, oxacillinase (OXA)-48, which was discovered in a clinical *K. pneumoniae* isolate in 2004, has been identified mostly in Mediterranean countries, especially Turkey [1,7].

In France, resistance of Enterobacteriaceae to carbapenems remains uncommon. According to data from the European Antimicrobial Resistance Surveillance Network (EARS-Net), the proportion of carbapenem-resistant strains among strains isolated from patients with invasive infections in 2009 was 0.03% (2 of 7,731) for *Escherichia coli* and 0.16% (2 of 1,268) for *K. pneumoniae* [8]. However, CPE isolates have already been described in France and were involved in sporadic cases or limited outbreaks [3,9-15].

Since 2001, a national Healthcare-Associated Infections Early Warning and Response System (HAI-EWRS) has been implemented in France to quickly detect unusual and emerging events in hospitals, promote outbreak investigations and implement control measures [16]. Healthcare facilities are mandatorily obliged to notify such events to interregional infection control coordinating centres (CClins), so they can receive technical assistance and to regional health authorities for the follow up of control measures. Notifications are then forwarded to the French Institute for Public Health

Surveillance (Institut de Veille Sanitaire, InVS) for second-line assistance and the monitoring of trends. For microbiological expertise, healthcare facilities can rely on a network of national reference centres (NRCs), funded and coordinated by InVS [17] or expert laboratories located in major university hospitals or research centres.

The objectives of this study were to review, quantify and describe the characteristics of CPE episodes reported to InVS during February 2004 (when the first CPE cases were notified) to 11 April 2011.

Methods

Definitions

We defined a case as a patient infected or colonised by a CPE that was confirmed by a reference or expert laboratory. The clinical diagnosis of infection or colonisation was made by the physician in charge of the patient.

An episode was defined as one sporadic case or several cases related by an identified chain of transmission. A chain of transmission was established between two or more cases if they had been in contact, i.e. they shared the same healthcare workers (nurse, auxiliary staff or physician).

Epidemiological investigation

We included all the episodes that were notified by healthcare facilities through the French HAI-EWRS. We also included other episodes that were retrospectively identified through a survey of French microbiologists known to have an interest and expertise in Enterobacteriaceae beta-lactamases, conducted by InVS by email in August 2010. Follow-up data on each notified episode were provided to InVS by CClins or laboratories.

For each episode, we documented the patients' demographic characteristics, number of infected or colonised patients, site of infection/colonisation, number of reported deaths, bacterial species, types of carbapenemase (as identified by the Antimicrobial Resistance NRC, based at the Institut Pasteur in Paris, or expert laboratories), existence of an epidemiological link between the index case and a foreign country, name of this country and the nature of the link (previous stay or hospitalisation abroad within one year of hospitalisation in France).

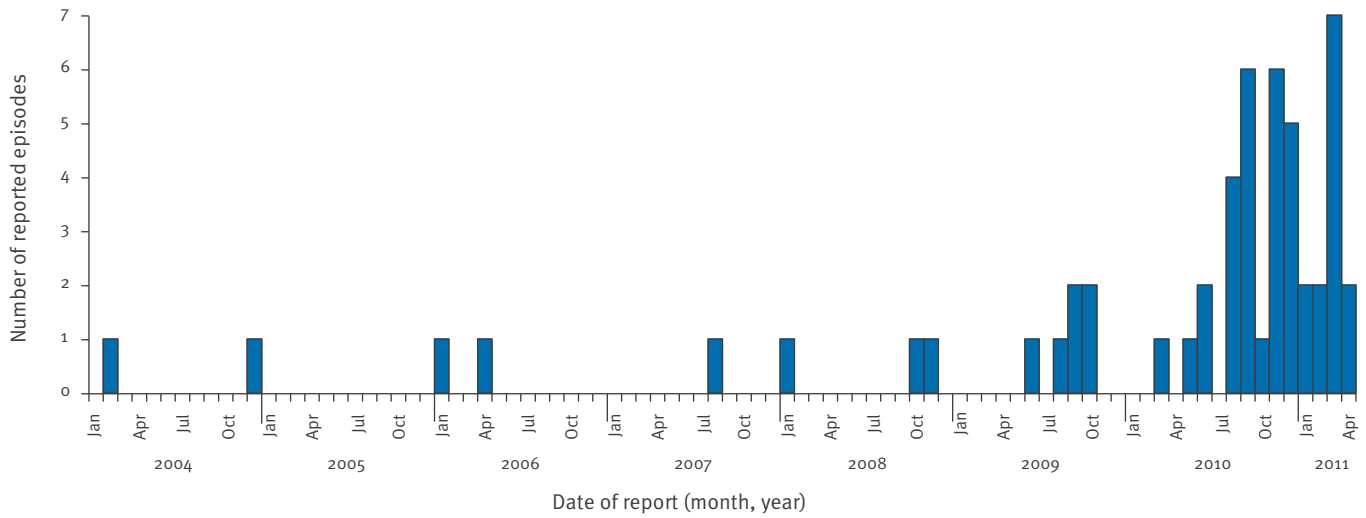
Microbiological investigations

Antibiotic susceptibility was tested by disc diffusion on Mueller-Hinton agar according to standards of the Antibiogram Committee of the French Microbiology Society [18].

In carbapenem-resistant strains, carbapenemase production was detected using Hodge test, and synergy test between carbapenems and ethylenediaminetetraacetic acid (EDTA) (for class B metallo beta-lactamases) or clavulanic acid (for class A beta-lactamases) [19]. The genes encoding carbapenemases were identified by the Antimicrobial Resistance NRC or 13 expert laboratories using PCR and sequencing of the amplified product [20]. In every PCR analysis, a positive control strain was included. All expert laboratories were located in major university hospitals or research centres and were involved in external quality assessment at the national level (through the French Health Products Safety Agency, Afssaps) or international level (through EARS-Net). The Antimicrobial Resistance NRC follows Institut Pasteur quality control policies.

Figure

Monthly number of episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011 (n=53)



Results

Number and location of CPE episodes

The first reported CPE episode occurred in France in February 2004 [12]. The yearly number of episodes remained low (1–3 episodes) until 2009, when a sharp increase was observed: 6, 26 and 13 episodes in 2009, 2010 and the first four months of 2011, respectively (Figure). A total of 53 CPE episodes were identified in France between February 2004 and April 2011, most of which (n=50) were reported through the HAI-EWRS.

These 53 episodes were reported in the following areas of France: Paris and the north of the country (n=36), south-east (n=8), east (n=4), west (n=3) and south-west (n=2).

Bacteria and resistance mechanisms

The CPE that were reported were mainly *K. pneumoniae* (n=33 episodes), but also *E. coli* (n=14), *Enterobacter cloacae* (n=6), *Enterobacter aerogenes* (n=3), *Citrobacter freundii* (n=2), *Serratia marcescens* (n=1) or *Proteus mirabilis* (n=1). Two or three species of Enterobacteriaceae were isolated in six episodes.

The carbapenemases involved in the 53 episodes were OXA-48 (n=23), KPC (n=16), VIM (n=6), NDM-1 (n=7) and VIM plus IMP (n=1) (Table 1).

Epidemiological description of the CPE episodes

The 53 episodes accounted for a total of 169 cases, comprising 52 infections and 112 colonisations (data available for 164 cases). Among the 169 cases, 43 deaths were reported, giving an estimated crude lethality rate (deaths of all cases, whether infected or colonised) of 25%.

Of the 53 episodes, 36 included a single, sporadic case. Secondary cases were reported in 18 episodes: the total number of cases in these 18 episodes ranged from 2 (in six episodes) to 32 (one episode). The mean number of cases by cluster was seven (median: four cases).

A total of 54 index cases were identified. In one episode, two co-index cases (two members of the same family repatriated at the same time) were reported. Of the 54 index cases with available information, 37 were found to be colonised, at least at one site: digestive tract (n=27 episodes), urinary tract (n=5), skin (n=2), respiratory tract (n=3) abdominal tract (n=1) or gynaecological tract (n=1). A total of 16 were infected at least at one site: urinary tract (n=6), respiratory tract (n=3), abdominal or gastrointestinal tract (n=5), bloodstream (n=3) and skin or soft tissue (n=1). The clinical diagnosis of infection or colonisation was not available for one index case and the clinical site was not available for two colonised and one infected index cases.

Episodes of particular importance

Several episodes were of particular importance, considering their impact on healthcare activities. In 2004, an outbreak of eight cases with VIM-1-producing *K. pneumoniae* (including five infections) occurred after the transfer of a patient from a Greek hospital. This outbreak, which lasted six months, was finally controlled after implementation of extended control and screening measures and led to the screening of 277 contact-patients [9,12]. In 2009, 13 cases with KPC-producing *K. pneumoniae* (two infections) were associated with a contaminated endoscope and transmission from patient to patient during healthcare in three hospitals. Controlling this outbreak also required implementation of extended control and screening measures and led to

Table 1

Bacterial species and carbapenemase type in 53 episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011

Bacterial species	Number of episodes by type of carbapenemase					Total
	OXA-48	KPC	NDM-1	VIM	VIM and IMP	
Klebsiella pneumoniae	12	14	3	4	0	**33**
Escherichia coli	9	1	3	1	0	**14**
Enterobacter cloacae	4	1	0	1	0	**6**
Enterobacter aerogenes	2	0	0	0	1	3
Citrobacter freundii	1	0	1	0	0	**2**
Proteus mirabilis	0	0	1	0	0	**1**
Serratia marcescens	1	0	0	0	0	**1**
Total	**23**[a]	**16**	**7**[b]	**6**	**1**	**53**[c]

IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Dehli metallo-beta-lactamase: OXA: oxacillinase; VIM: Verona integron-encoded metallo-beta-lactamase.

[a] OXA-48 was involved in four episodes with two bacterial species and in one episode with three species.

[b] NDM-1 was involved in one episode with two bacterial species isolated from patients with a possible epidemiological link.

[c] Five episodes involved two species with the same carbapenemase and one episode involved three species with the same carbapenemase.

the screening of 341 contact-patients in five healthcare facilities. The index case was a patient transferred from Greece [14,21]. In 2010, an outbreak of 13 cases with OXA-48-producing *K. pneumoniae* (seven infections) led to the screening of more than 280 contact-patients in 15 healthcare facilities. Interestingly, the index case in this episode did not report any travel abroad [22]. In addition, an ongoing episode of OXA-48-producing *K. pneumoniae*, which was notified in November 2010, has included 32 cases (infections or colonisations) to date and has led to the screening of contact-patients in more than 10 healthcare facilities.

Seven episodes were associated with NDM-1-mediated carbapenem-resistance: five were reported in 2010 and two during the first three months of 2011. In these seven episodes, there were six index cases who reported travel within the previous year to India and one to Iraq [23-25]. Five were hospitalised abroad before their transfer to a French hospital. Two lived in India and had received healthcare in France, but had no reported hospitalisation in India within the previous year. Nine cases were associated with these episodes; the bacterial species involved are reported in Table 1. No deaths were reported.

Association with cross-border transfer

Of the 53 episodes, 42 were associated with cross-border transfers: the index cases had been transferred directly from a foreign hospital to a French hospital (n=27 episodes), or had been hospitalised in a foreign hospital a few days (n=1), a few weeks (n=1), between one and six months (n=4) or one year (n=1) before their hospitalisation in France. In three additional episodes, the index cases lived abroad and had no reported hospitalisation in the previous year (two of the index cases were colonised; the other was infected). In the other five episodes, the index cases had spent weeks or months in a foreign country before their hospitalisation in France, but without any reported hospitalisation abroad. These five index cases were colonised.

In the 42 episodes associated with cross-border transfers, the countries where index cases had travelled, been hospitalised or had lived were Greece (n=14 episodes), Morocco (n=7), India (n=6), Italy (n=4), Algeria (n=3), Tunisia (n=2), Egypt (n=2), Turkey (n=2), United States (n=1) and Iraq (n=1). Of the 14 episodes involving cross-border transfer with North Africa (Morocco, Algeria, Tunisia and Egypt), 12 were associated with OXA-48-producing bacteria (Table 2).

In 11 of the 53 episodes, the index cases had not travelled, been hospitalised or lived in a foreign country, before their hospitalisation in France. Among these index cases, one was reported from Réunion. The majority of these episodes (n=9) were associated with OXA-48 carbapenemase (Table 2).

Discussion and conclusion

Although national surveillance data demonstrate that Enterobacteriaceae resistance to carbapenems remains rare in France, our study, based on HAI-EWRS notifications and a survey among French microbiologists, strongly suggests that CPE are emerging in French healthcare facilities and have an important impact on the organisation of health care. It also demonstrates the ability of the French HAI-EWRS to detect unusual and emerging events in hospitals, since a large majority of CPE episodes have been reported through this

Table 2

Carbapenemase type in 53 episodes of carbapenemase-producing Enterobacteriaceae infection or colonisation, France, 1 January 2004–11 April 2011, by country where index cases had been hospitalised or stayed abroad

Country	Number of episodes[a] by type of carbapenemase					Total
	OXA-48	KPC	NDM-1	VIM	VIM and IMP	
Greece	0	11 (2007)	0	3 (2004)	0	**14**
Morocco	7 (2010)	0	0	0	0	**7**
India	0	0	6 (2010)	0	0	**6**
Italy	0	2 (2010)	0	2 (2008)	0	**4**
Algeria	1 (2010)	1 (2010)	0	1 (2008)	0	**3**
Tunisia	2 (2011)	0	0	0	0	**2**
Egypt	2 (2009)	0	0	0	0	**2**
Turkey	2 (2010)	0	0	0	0	**2**
Iraq	0	0	1 (2010)	0	0	**1**
United States	0	1 (2006)	0	0	0	**1**
No stay or hospitalisation abroad reported	9 (2010)	1 (2010)	0	0	1 (2004)	**11**
Total	**23**	**16**	**7**	**6**	**1**	**53**

IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Dehli metallo-beta-lactamase: OXA: oxacillinase; VIM: Verona integron-encoded metallo-beta-lactamase.

[a] The years in parentheses are the year the first case in this study was reported.

system. The effectiveness of HAI-EWRS has also been demonstrated with other emerging pathogens in the recent past [26-28].

In this survey of CPE episodes notified in France, most of the reported episodes comprised sporadic cases and were related to cross-border transfer, mainly after hospitalisation in countries abroad where CPE are endemic. OXA-48 was the most frequent type of carbapenemase and was often associated with index cases who had been previously hospitalised in North Africa and Turkey. The second most frequent carbapenemase was KPC, which was often associated with index cases previously hospitalised in Greece. The types of carbapenemase observed by country of origin for index cases are highly consistent with those previously described in these countries: NDM-1 in the Indian subcontinent [5,23], KPC notably in Greece and the United States [3,4], OXA-48 in Turkey [29,30], Tunisia [31] and Morocco [32]. In Greece, the proportion of carbapenem-resistant strains among *K. pneumoniae* increased from 27.8% to 43.5% during 2005 to 2009 [8]. Interestingly, the origin of index cases was also highly consistent with population migration routes and countries most frequently visited by French tourists [33].

As cross-border transfer and globalisation are major trends in the world today, awareness of the risk of spread of multidrug resistance, such as carbapemenase-mediated resistance of Enterobacteriaceae by cross-border transfer of patients, needs to be emphasised. Furthermore, appropriate control measures need to be strongly reinforced in countries where carbepenemase-producing Enterobacteriaceae are endemic [34,35]. In addition, in order to prevent or to delay emergence of carbapenemase-mediated resistance in countries with low prevalence, such as France, it is essential to rapidly identify CPE by screening carriers among patients transferred from hospitals in countries with high prevalence of these organisms and to implement adequate control measures.

In response to the trends observed, the French Healthcare Safety Advisory Committee issued in 2010 national recommendations for screening and presumptive isolation with contact precautions of patients transferred from or hospitalised abroad. These recommendations target two multidrug-resistant pathogens with a low prevalence in France (vancomycin-resistant enterococci, VRE, and CPE). Healthcare facilities are requested to notify immediately CClins and regional health authorities about any suspected episodes of VRE or CPE infection/colonisation and laboratories should send strains to the Antimicrobial Resistance NRC or an expert laboratory for confirmation [36]. If a case is confirmed, adequate control measures should be rapidly implemented: reinforcement of standard and contact precautions, contact tracing and cohorting of patients into three distinct sectors (one for cases, one for contact-patients and one for newly admitted VRE- or CPE-free patients) [36,37]. Such a strict strategy of cohorting patients – which had been developed and field-tested in healthcare facilities that experienced the first CPE outbreaks and was later disseminated through national recommendations – has limited the number of secondary cases and has led to the control of CPE outbreaks [9,21].

In 11 of the 53 reported episodes, the index cases had not crossed any border. Nine of the 11 were due to OXA-48 carbapenemase. Although a chain of transmission resulting from contact with an unknown traveller from abroad could have been missed, the beginning of autochthonous circulation of CPE in France cannot be excluded. Almost all of these 11 episodes (n=10) have been reported since 2010: this recent trend emphasises the need for sustained vigilance when carbapenem resistance is suspected in Enterobacteriaceae isolated from any patient. Moreover, it also underlines the need for better antimicrobial stewardship in France. In French healthcare facilities, carbapenem consumption increased from 2.0 defined daily doses per 1,000 bed-days in 1999 to 4.8 per 1,000 in 2009 (P. Cavalié, Afssaps, personal communication, November 2010) and is most probably related to the spread of Enterobacteriaceae producing extended-spectrum beta-lactamases [8].

Our study has some limitations. First, the completeness of reporting cannot be guaranteed since (i) all French healthcare facilities do not have the capacity to identify patients with CPE and should therefore rely on the help of the Antimicrobial Resistance NRC or an expert laboratory, (ii) some healthcare facilities may not report them (despite reporting being mandatory and strongly encouraged) and (iii) data collected through HAI-EWRS could be incomplete. Conversely, recent emphasis on CPE in the scientific literature, national recommendations and media reports could have triggered better reporting and may partly explain the sharp increase in the number of reported episodes observed in 2010.

Second, the impact of CPE on patients' morbidity or mortality is difficult to assess. The crude mortality rate of cases in this study was high, as was reported in outbreaks with extended-spectrum beta-lactamase-producing Enterobacteriaceae [38,39]. However, crude estimates of lethality are not easy to interpret because of the difficulties in ascertaining retrospectively the cause of deaths in patients with multiple pathologies, and as it is not known whether the patients who died had been infected or colonised.

Last, six episodes involved more than one bacteria species with the same resistance mechanism, but no microbiological data were available that could account for this. Such bacteria could have been identified among the same or different patients and, as reported previously, interspecies transmission of carbapenemase genes by transposons or by self-transferable plasmids could have occurred [40].

Improving coordination between the Antimicrobial Resistance NRC and expert laboratories, healthcare facilities and InVS in the surveillance of CPE should allow episodes to be better documented, future trends to be monitored and the impact of current national recommendations to be assessed.

In conclusion, emergence of CPE in France, Europe and worldwide is nowadays a major medical and public health concern because it may lead to therapeutic dead-ends. The French HAI-EWRS demonstrated to be an effective tool to detect and monitor CPE emergence and to promote adequate recommendations for control. To date, most of episodes reported in France have been associated with a sporadic case who had been hospitalised, had travelled or had lived in foreign countries where CPE are prevalent.

The need to contain CPE emergence in France justifies reinforcing control measures when there is cross-border transfer. However, such measures might have a limited impact in the long term if no similar measures are implemented to control the sources abroad. Increasing laboratories' capacities, infection control and antimicrobial stewardship at a global level is therefore urgently needed for a successful fight against this new type of antimicrobial resistance.

Acknowledgments

We thank all healthcare professionals, infection control units, healthcare facilities and microbiological laboratories involved in the study, Patrice Nordmann (Service de Bactériologie-Virologie-Hygiène, Inserm U914, Le Kremlin-Bicêtre) for strain characterisation in some of the episodes notified by healthcare facilities and Philippe Cavalié (Afssaps) for national data on carbapenem consumption.

RAISIN (Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales) Group participants
S. Alleaume (InVS, Saint-Maurice), C. Bernet (CClin Sud-Est, Lyon), I. Poujol (InVS, Saint-Maurice), H. Sénéchal (CClin Ouest, Rennes), L. Simon (CClin Est, Nancy), AG. Venier (CClin Sud-Ouest, Bordeaux).

Expert Laboratories Group participants
A. Andremont (Antimicrobial Resistance National Reference Centre, Resistance in commensal flora Associated Laboratory, Hôpital Bichat, Paris), G. Arlet (Laboratoire de Bactériologie, Pierre et Marie Curie (Paris 6) University, Paris), R. Bonnet (Laboratoire de Microbiologie, Centre Hospitalier Universitaire, Clermont-Ferrand), C. de Champs (Laboratoire de Microbiologie, Centre Hospitalier Universitaire, Reims), S. Corvec (Laboratoire de Microbiologie, Centre Hospitalier Universitaire, Nantes), P. Courvalin (Antimicrobial Resistance National Reference Centre, Institut Pasteur, Paris), K. Jeannot (Antimicrobial Resistance National Reference Centre, Institut Pasteur, Paris), J.P. Lavigne (Laboratoire de Microbiologie, Centre Hospitalier Universitaire, Nîmes), A. Lozniewski (Laboratoire de Microbiologie, Centre Hospitalier Universitaire, Nancy), M.H. Nicolas-Chanoine (Service de Microbiologie, Hôpital Beaujon, Clichy), I. Podglajen (Service de Microbiologie, Hôpital Européen Georges Pompidou, Paris), C. Quentin (Laboratoire de Microbiologie, Université de Bordeaux 2 - UMR CNRS 5234, Bordeaux), J.M. Rolain (URMITE CNRS-IRD UMR 6236, Faculté de Médecine et de Pharmacie, Marseille), W. Sougakoff (INSERM UMRS 872-12, Pierre et Marie Curie (Paris 6) University, Paris).

References

1. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev. 2007(3);20:440-58.
2. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob Agents Chemother. 2001;45(4):1151-61.
3. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis. 2009;9(4):228-36.
4. Pournaras S, Protonotariou E, Voulgari E, Kristo I, Dimitroulia E, Vitti D, et al. Clonal spread of KPC-2 carbapenemase-producing Klebsiella pneumoniae strains in Greece. J Antimicrob Chemother. 2009;64(2):348-52.
5. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010(9);10:597-602.
6. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother. 2009;53(12):5046-54.
7. Poirel L, Naas T, Nordmann P. Diversity, epidemiology, and genetics of class D beta-lactamases. Antimicrob Agents Chemother. 2010;54(1):24-38.
8. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2009. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2010. Available from: http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=580
9. Kassis-Chikhani N, Saliba F, Carbonne A, Neuville S, Decre D, Sengelin C, et al. Extended measures for controlling an outbreak of VIM-1 producing imipenem-resistant Klebsiella pneumoniae in a liver transplant centre in France, 2003-2004. Euro Surveill. 2010;15(46):pii=19713. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19713
10. Barbier F, Ruppé E, Giakkoupi P, Wildenberg L, Lucet J, Vatopoulos A, et al. Genesis of a KPC-producing Klebsiella pneumoniae after in vivo transfer from an imported Greek strain. Euro Surveill. 2010;15(1):pii=19457. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19457
11. Biendo M, Canarelli B, Thomas D, Rousseau F, Hamdad F, Adjide C, et al. Successive emergence of extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacter aerogenes isolates in a university hospital. J Clin Microbiol. 2008;46(3):1037-44.
12. Kassis-Chikhani N, Decré D, Gautier V, Burghoffer B, Saliba F, Mathieu D, et al. First outbreak of multidrug-resistant Klebsiella pneumoniae carrying blaVIM-1 and blaSHV-5 in a French university hospital. J Antimicrob Chemother. 2006;57(1):142-5.
13. Kassis-Chikhani N, Decré D, Ichai P, Sengelin C, Geneste D, Mihaila L, et al. Outbreak of Klebsiella pneumoniae producing KPC-2 and SHV-12 in a French hospital. J Antimicrob Chemother. 2010;65(7):1539-40.
14. Naas T, Cuzon G, Babics A, Fortineau N, Boytchev I, Gayral F, et al. Endoscopy-associated transmission of carbapenem-resistant Klebsiella pneumoniae producing KPC-2 beta-lactamase. J Antimicrob Chemother. 2010;65(6):1305-6.
15. Petrella S, Ziental-Gelus N, Mayer C, Renard M, Jarlier V, Sougakoff W. Genetic and structural insights into the dissemination potential of the extremely broad-spectrum class A beta-lactamase KPC-2 identified in an Escherichia coli strain and an Enterobacter cloacae strain isolated from the same patient in France. Antimicrob Agents Chemother. 2008(10);52:3725-36.
16. 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

17. Institut de Veille Sanitaire (InVS). Centres nationaux de référence (CNR). [National Reference Centres (NRC)]. Saint-Maurice: InVS. French. [Accessed 26 May 2011]. Available from : http://www.invs.sante.fr/surveillance/cnr/
18. Société Française de Microbiologie (SFM). Comité de l'antibiogramme de la Société Française de Microbiologie. Recommandations 2011 [Antibiogram committee of the French Society for Microbiology. Recommendations 2011]. Paris: SFM: 2011. French.
19. Picão RC, Andrade SS, Nicoletti AG, Campana EH, Moraes GC, Mendes RE, et al. Metallo-beta-lactamase detection: comparative evaluation of double-disk synergy versus combined disk tests for IMP-, GIM-, SIM-, SPM-, or VIM-producing isolates. J Clin Microbiol. 2008;46(6):2028-37.
20. Courvalin P, Leclercq R, Rice LB, editors. Antibiogram. Washington DC: American Society for Microbiology Press: 2010.
21. Carbonne A, Thiolet JM, Fournier S, Fortineau N, Kassis-Chikhani N, Boytchev I, et al. Control of a multi-hospital outbreak of KPC-producing Klebsiella pneumoniae type 2 in France, September to October 2009. Euro Surveill. 2010;15(48):pii=19734. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19734
22. Cuzon G, Ouanich J, Gondret R, Naas T, Nordmann P. Outbreak of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in France. Antimicrob Agents Chemother. 2011;55(5):2420-3.
23. Struelens MJ, Monnet DL, Magiorakos AP, Santos O'Connor F, Giesecke J, European NDM-1 Survey Participants. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. Euro Surveill. 2010;15(46):pii=19716. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19716
24. Poirel L, Fortineau N, Nordmann P. International transfer of NDM-1-producing Klebsiella pneumoniae from Iraq to France. Antimicrob Agents Chemother. 2011;55(4):1821-2.
25. Poirel L, Ros A, Carricajo A, Berthelot P, Pozzetto B, Bernabeu S, et al. Extremely drug-resistant Citrobacter freundii isolate producing NDM-1 and other carbapenemases identified in a patient returning from India. Antimicrob Agents Chemother. 2011;55(1):447-8.
26. Bourdon N, Fines-Guyon M, Thiolet JM, Maugat S, Coignard B, Leclercq R, et al. Changing trends in vancomycin-resistant enterococci in French hospitals, 2001-08. J Antimicrob Chemother. 2011;66(4):713-21.
27. Coignard B, Barbut F, Blanckaert K, Thiolet JM, Poujol I, Carbonne A, et al. Emergence of Clostridium difficile toxinotype III, PCR-ribotype 027-associated disease, France, 2006. Euro Surveill. 2006;11(37):pii=3044. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3044
28. Naas T, Coignard B, Carbonne A, Blanckaert K, Bajolet O, Bernet C, et al. VEB-1 Extended-spectrum beta-lactamase-producing Acinetobacter baumannii, France. Emerg Infect Dis. 2006;12(8):1214-22.
29. Carrër A, Poirel L, Eraksoy H, Cagatay AA, Badur S, Nordmann P. Spread of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in Istanbul, Turkey. Antimicrob Agents Chemother. 2008;52(8):2950-4.
30. Carrër A, Poirel L, Yilmaz M, Akan OA, Feriha C, Cuzon G, et al. Spread of OXA-48-encoding plasmid in Turkey and beyond. Antimicrob Agents Chemother. 2010;54(3):1369-73.
31. Cuzon G, Naas T, Lesenne A, Benhamou M, Nordmann P. Plasmid-mediated carbapenem-hydrolysing OXA-48 beta-lactamase in Klebsiella pneumoniae from Tunisia. Int J Antimicrob Agents. 2010;36(1):91-3.
32. Benouda A, Touzani O, Khairallah MT, Araj GF, Matar GM. First detection of oxacillinase-mediated resistance to carbapenems in Klebsiella pneumoniae from Morocco. Ann Trop Med Parasitol. 2010;104(4):327-30.
33. Ministère de l'économie des finances et de l'industrie. Voyages personnels. Répartition des voyages et nuitées personnels à l'étranger par pays de destination (2008). [Personal travel. Distribution of personal trips and overnight stays abroad by country of destination (2008)]. 2009. French. Available from: http://www.tourisme.gouv.fr/stat_etudes/memento/2009/p83.pdf
34. Coignard B. Cross-border transfer of patients with multidrug-resistant microorganisms in Europe [abstract 704]. Fifth Decennial International Conference on Healthcare-Associated Infections 2010, Atlanta, GA, 18-22 Mar 2010.
35. Wernli D, Haustein T, Conly J, Carmeli Y, Kickbusch I, Harbarth S. A call for action: the application of the international health regulations to the global threat of antimicrobial resistance. PLoS Med. 2011;8(4):e1001022.
36. Haut Conseil de la Santé Publique. Commission spécialisée Sécurité des patients: infections nosocomiales et autres évènements indésirables liés aux soins et aux pratiques. Maîtrise de la diffusion des bactéries multirésistantes aux antibiotiques importées en France par des patients rapatriés ou ayant des antécédents d'hospitalisation à l'étranger [Control of multidrug-resistant bacteria imported into France from patients repatriated or with a history of hospitalisation abroad]. Nov 2010. French. Available from: http://www.hcsp.fr/docspdf/avisrapports/hcspr20101116_bmrimport.pdf
37. Haut Conseil de la santé publique. Commission spécialisée Sécurité des patients: infections nosocomiales et autres évènements indésirables liés aux soins et aux pratiques. Rapport relatif à la maîtrise de l'émergence et de la diffusion des entérocoques résistants aux glycopeptides (ERG) dans les établissements de santé français [Control of the emergence of glycopeptide-resistant enterococci in French healthcare facilities]. March 2010. French. Available from: http://www.hcsp.fr/docspdf/avisrapports/hcspr20090219_ERG.pdf
38. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29(12):1099-106.
39. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. Clin Infect Dis. 2006;42 Suppl 4:S164-72.
40. Drieux L, Bourgeois-Nicolaos N, Cremmiter J, Lawrence C, Jarlier V, Doucet-Populaire F, et al Accumulation of carbapenemase producing Gram-negative bacteria in a single patient linked to the acquisition of multiple carbapenemase producers and to the vivo transfer of plasmid encoding VIM-1. Int J Antimicrob Agents. 2011 May 12. [Epub ahead of print].

Clusters of infectious diseases in German nursing homes – observations from a prospective infection surveillance study, October 2008 to August 2009

M Schulz (math.schulz@googlemail.com)[1], M Mielke[1], N Wischnewski[1]
1. Division Applied Infection Control and Hospital Hygiene, Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany

Citation style for this article:
Schulz M, Mielke M, Wischnewski N. Clusters of infectious diseases in German nursing homes – observations from a prospective infection surveillance study, October 2008 to August 2009.
Euro Surveill. 2011;16(22):pii=19881. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19881

Article published on 2 June 2011

A prospective infection surveillance study was carried out among residents of seven nursing homes in and around Berlin, Germany, from October 2008 to August 2009. A considerable number of infections were found to occur in clusters. Active surveillance was carried out using pre-established case definitions of infections in nursing homes (McGeer criteria). Case finding was based on routine nursing files. Infection rates were calculated per 1,000 resident days. Clusters were identified using a pre-established definition. In total 511 residents were observed during 74,626 resident days (rd), and 393 infections occurred in 243 participants, giving an overall incidence of infection of 5.3 per 1,000 rd. The most common infections were gastrointestinal infections (n=122; 1.6/1,000 rd), acute respiratory disease (n=86; 1.2/1,000 rd) and urinary tract infections (n=71; 1.0/1,000 rd). Seven clusters involving 74 infections in 57 residents were observed: three of acute respiratory disease, three of acute gastrointestinal disease and one of conjunctivitis. Attack rates varied between 11% and 61%. Clusters occurred frequently in the observed nursing homes and could be detected by infection surveillance based on routine documentation.

Background

Clusters of infectious diseases can have major impact on healthcare facilities resulting in increased morbidity and mortality [1]. Nursing homes pose unique challenges in early cluster identification and control as elderly people often present with atypical signs of disease. They are also likely to develop a more severe course of disease, often requiring hospitalisation [2-4]. Delivery of care can be compromised by associated illness and absenteeism among staff [5]. We focus here on clusters of acute respiratory disease (ARD) and gastrointestinal disease (GID) as these seem to predominate in this setting [1].

Up to 60% of residents can be affected during outbreaks in nursing homes [6,7], many of whom develop complications or suffer functional decline [8]. Case fatality rates as high as 30–55% have been observed in clusters of ARD [7,9,10].

A wide range of viruses have been identified as aetiological agents of ARD in nursing homes [11], including influenza viruses, respiratory syncytial virus, rhinovirus and human metapneumovirus. The spectrum of bacteria causing outbreaks of pneumonia in nursing homes includes *Bordatella pertussis*, *Streptococcus pneumoniae* and *Legionella pneumophila*. Multiple routes of transmission have been identified in bacterial outbreaks such as staff-to-resident transmission and transmission via contaminated environment. Viral outbreaks preceding outbreaks of bacterial pneumonia have been described [12], leading to prolonged illness.

Another common problem among residents of long-term care facilities is GID [13]. The aetiology of diarrhoea and/or vomiting in the elderly may be non-infectious, a fact that can complicate the detection of communicable GID in nursing homes [13]. In infectious GID, viruses frequently are the causative agents, most notably norovirus, but also bacterial outbreaks of gastrointestinal disease have been reported [14-16]. *Clostridium difficile* seems to play an increasing role in diarrhoeal disease in nursing homes and outbreaks have been reported [17]. Other infectious diseases that have caused outbreaks in long-term care facilities include conjunctivitis, scabies and skin infections [1].

Prospective surveillance for infections was carried out among residents of seven nursing homes in and around Berlin. As a considerable number of infections turned out to occur in clusters, these clusters are described here in more detail, and we estimate their impact on total infection rates.

Methods

In each of seven nursing homes in Germany, a prospective infection surveillance study was carried out over a period of six months between October 2008 and August 2009. The nursing homes were situated in or near Berlin. The project was introduced during lectures for nursing home personnel responsible for hygienic matters. Interested institutions were included if

they fulfilled the following criteria: institutions with a majority of elderly (>75 years) permanent residents, for whom constant supervision and nursing care are provided. Specialised facilities (e.g. facilities for mentally handicapped residents or for patients needing assisted ventilation) were excluded. The study included only residents who were in a stable medical condition, did not need constant specialised care (e.g. assisted ventilation) and showed no signs of infection at the start of the observation period. Residents newly admitted to the nursing home during the observation period were also asked to participate (open cohort study).

Data collection and case finding

At the beginning of the study, we collected for all participants demographic data, diagnosis of chronic diseases, score on the Braden scale (a multidimensional scoring system assessing a person's functional status in order to estimate the risk of developing pressure ulcers) and information on currently used medical devices such as urinary catheters.

Infections were identified either by the attending physician or by abstracting data from nursing files using previously described definitions for infection surveillance in long-term care patients (McGeer criteria) [18]. Residents' charts were reviewed for signs and symptoms of infection every second week by two external doctors. Antibiotic treatment and microbiological results that had been ordered by the attending physician were documented to further characterise infections. The study was observational only and no attempt was made to influence the routine documentation of physicians or nurses.

Cluster analysis

A cluster was defined as infections of the same type according to the applied criteria for infection (McGeer criteria) affecting at least 10% of the study population within a time span of 21 days. As the case definitions of influenza-like illness, bronchitis and pneumonia are similar these diagnoses were combined as ARD.

One cluster of respiratory infections was characterised by a high attack rate and case fatality rate. In a retrospective cohort study of that cluster, additional data for all residents living in the affected nursing home were collected using routine documentation.

Cases in this cluster were defined as all residents fulfilling, between 15 December 2008 and 15 February 2009, the following case definition: two or more of the following symptoms: body temperature higher than 37.5 °C, acute cough, acute shortness of breath, deteriorating mental or functional status. Absenteeism among staff was estimated using sick-reports.

Ethical considerations

The regional committee for medical research ethics consented to the study. The study did not entail any direct contact with patients. Residents or their legal guardians had to give informed consent in order to participate.

Statistical analyses

All data were analysed using the statistical programmes Epi Info version 3.5.1 and OpenEpi. Incidences of infection were calculated as the number of infections per 1,000 resident days (rd), (days that a resident is actually present in the home and not infected). The 95% confidence interval (CI) for infection rates was calculated using Mid-P exact test with Miettinen's modification as described elsewhere [19]. The odds ratio was calculated as described by Martin et al. [20].

Results

Seven nursing homes participated in this prospective cohort study, all situated in or near Berlin. In total 408 residents entered the study on day 1. Another 102 residents were enrolled at various points later during the

Table 1

Characteristics of facilities and patient cohorts, infection incidence study, Germany, October 2008–August 2009

Nursing home	A	B	C	D	E	F	G	Total
Period of observation	Oct 08–Mar 09	Dec 08–May 09	Dec 08–May 09	Mar 09–Aug 09	Mar 09–Aug 09	Feb 09–Jul 09	Mar 09–Aug 09	Oct 08–Aug 09
Number of beds	40	28	115	108	56	115	196	658
Number of wards	1	1	3	5	2	3	7	22
Residents day 1	38	28	105	104	54	113	130	572
Bed occupancy rate day 1 (%)	95	100	91	96	96	98	66	87
Participants day 1	38	28	68	61	36	47	130	408
Participation rate day 1 (%)	100	100	65	59	67	42	100	71
Total number of participants	44	36	72	63	36	49	211	511
Resident days[a]	6,951	4,691	10,853	10,483	6,541	8,151	26,956	74,626
Deaths during study	6	9	15	7	1	4	37	79
Termination of study due to other reasons	1	0	1	1	0	1	6	9

[a] Days on which a resident is present in the nursing home and not infected.

study. Seventy-nine of the 506 participating residents died during the study and nine moved away from their nursing home. Data about the facilities are presented in Table 1. In one nursing home (G) medical care was provided by one physician based in the facility. In the remaining nursing homes medical care was provided by various community-based general practitioners.

From October 2008 to August 2009, 511 residents with 74,626 rd were observed. The mean age of residents was 85 years (median 86 years, range 31-104 years), and 410 (80%) were female. The median length of stay of residents in their respective nursing home was 1.6 years. Some 134 residents (26%) had diabetes mellitus and 62 (12%) of them were insulin-dependant. Thirty-eight patients (7%) suffered from chronic obstructive pulmonary disease. Twenty-eight (5%) had pressure sores and 12 (2%) leg ulcers. Thirty-six (7%) had a urinary catheter and 20 (4%) an enteral feeding tube. Some 314 (61%) of the residents were to some degree disoriented in time or space. In total 282 (55%) could walk independently, 187 (37%) were dependant on a wheelchair and 40 (8%) were bedridden.

Overall infection rate

A total of 393 infections occurred in 243 participants. The overall incidence of infection was 5.3 per 1,000 rd (95% CI: 4.77–5.81). Nursing home-specific incidence rates varied considerably (range: 3.0–13.4/1,000 rd). The most common infections were gastrointestinal (n=122; 1.6/1,000 rd; 95% CI: 1.36–1.94), acute respiratory disease (n=86; 1.2/1,000 rd; 95% CI: 0.93–1.42), urinary tract (n=71; 1.0/1,000 rd; 95% CI: 0.75–1.19), viral and bacterial conjunctivitis (n=35; 0.5 /1,000 rd; 95% CI: 0.32–0.65), common cold (n=27; 0.4/1,000 rd; 95% CI: 0.24–0.52) and soft tissue infection (n=24; 0.3/1,000 rd; 95% CI 0.21– 0.47).

Clusters of infection

Seven clusters could be identified in four of the seven observed nursing homes (Table 2), three ARD clusters, three GID clusters and one of infectious conjunctivitis. Clusters of other diseases such as skin infections or urinary tract infections could not be identified.

Six clusters occurred in winter months, five of them in January. Attack rates based on case finding using McGeer criteria varied between 11% and 60% (Table 2). The contribution of infections occurring in clusters to the overall infection incidence rate was 19%. Some 31 ARD infections (36%), 38 GID infections (31%) and five conjunctivitis infections (14%) occurred in clusters. We systematically recorded the microbiological probes ordered by the attending physicians and to our knowledge, only one cluster (G-GID) was investigated further with microbiological methods. Thirteen GID cases occurred in one ward in nursing home G between 2 and 5 May, and norovirus was identified in the stool of three symptomatic residents.

One cluster of ARD (B-ARD) showed high attack and case fatality rates. The population of the affected nursing home (B) consisted of 29 very old women (mean age 91 years). They were moderately impaired according to the Braden scale (n=21 at low risk), with few underlying diseases. Only one resident had a medical device (urinary catheter). Fifteen nurses and three community-based general practitioners provided medical care to the residents. All resident rooms were single rooms with shower and toilet.

The first case of respiratory infection among the residents of nursing home B occurred on 11 January 2009. In total, 19 of 29 residents fulfilled the case definition, all within seven days after onset of disease in the index case. The epidemiological curve shows a sharp rise of new infections on two subsequent days. Six of the affected residents died, all within 10 days after presentation of first signs of illness. Seven residents had to be hospitalised and another eight received systemic antibiotic treatment as prescribed by their general practitioner. The cluster stopped within seven days without specific control measures. To our knowledge no attempt was made to isolate an aetiological agent.

Table 2

Time span, type of infection and attack rates for clusters of infections, nursing homes, Germany, October 2008–August 2009

Nursing home	Disease	First case(date)	Last case (date)	Number of cases	Number of exposed	Attack rate
A	Acute respiratory disease (A-ARD)	18 Jan 2009	26 Jan 2009	6	38	16%
A	Gastrointestinal disease (A-GID)	21 Jan 2009	31 Jan 2009	9	38	24%
B	Acute respiratory disease (B-ARD)[a]	15 Jan 2009	24 Jan 2009	13	28	46%
B	Gastrointestinal disease (B-GID)[a]	17 Jan 2009	8 Feb 2009	17	28	61%
B	Conjunctivitis (B-Con)	9 Jan 2009	10 Jan 2009	5	28	18%
C	Acute respiratory disease (C-ARD)	10 Jan 2009	26 Jan 2009	12	72	17%
G	Gastrointestinal disease (G-GID)	2 May2009	3 May 2009	12	29	41%

[a] Clusters which were further analysed

Seventeen of the 29 residents had received seasonal influenza immunisation in the autumn of 2008. There was no significant difference in the number of cases or case fatality rate between the vaccinated and the unvaccinated group. No significant risk factor could be identified for development of disease. A lower score on the Braden scale (i.e. greater functional disability) and incontinence were factors significantly associated with fatal outcome (Table3).

Concomitantly with this respiratory cluster, a cluster of gastrointestinal disease occurred in nursing home B, which affected both staff and residents. Overall, 17 residents were sick and presented primarily with vomiting and diarrhoea. Five of the residents affected by GID also suffered from ARD. In addition, seven of 15 staff members reported sick with ARD or GID during the cluster. The first three cases of ARD among staff members occurred before the first case among residents. No fatal cases occurred among staff members.

Discussion

Although clusters of infections in nursing homes have been widely described, the systematic recognition of increased rates of certain diseases is hampered by the lack of established infection surveillance systems. Furthermore, systematic laboratory investigations of infections or clusters of infection in the context of prospective infection surveillance studies are rare in this setting. When surveilling the population of seven nursing homes for the development of infections we identified seven clusters of infections including one with high attack rate and mortality. The spectrum of clusters included acute respiratory disease, gastrointestinal disease and conjunctivitis. This is in accordance with the patterns described in the published literature [1,2,7,11,13,14].

Only one cluster of gastrointestinal disease was investigated microbiologically and norovirus was detected in the stool of three symptomatic residents. In this nursing home (G), medical care was provided by a nursing home-based physician, for whom it may be easier to recognise higher rates of infection among the residents.

Due to the high number of affected residents as well as the severity of the disease, one outbreak of ARD was investigated in more detail. Although no aetiological agent was identified, we assume that viral pulmonary disease was the most probable cause of the cluster, based on the rapid spread of disease, the high case fatality rate and the fact that both residents and staff members were affected. It can be assumed that the very high age of the population (mean age 91 years) has contributed to the high mortality rate. As resident-to-resident contact was limited within the institution, staff-to-resident transmission could have been an important mode of transmission [21]. As exact information concerning start and duration of illness among staff members could not be obtained, we were not able to fully investigate this question. The cluster was further complicated by a concurrent cluster of gastrointestinal disease.

Study limitations

Since any intervention including systematic microbiological analyses was beyond the scope of this study, aetiological diagnosis could only be based upon diagnostic steps taken by the attending physicians. In addition, the evaluation of infection control measures during a cluster was beyond the scope of this study. As documentation was not standardised and the vigilance of nurses was not influenced in an active way infections with minor symptoms may have been underreported, which may explain the relative low incidence of common cold. During clusters staff awareness could be higher, resulting in increased reporting and documentation of symptoms. Thus the contribution of clustered infections to overall infection rates could have been overestimated. Furthermore, inter-facility comparison of infection rates cannot be performed because documentation was not standardised and the periods of observation (seasonality) were different.

Conclusions

Infection surveillance based on routine nursing files can detect clusters of infections, enabling staff to report them to infection control professionals quickly. However, there is need to educate staff at the point of care in order to fully take advantage of this possibility [22,23]. Training should aim at standardising symptom documentation and at the correct evaluation of the documentation by designated staff members. In our experience the weekly surveillance of nursing files takes a few hours and could be performed by a quality assurance representative or a nurse in charge of hygienic matters.

Clinical features of infections are often unspecific and cannot usually be used to identify aetiology [2]. Therefore nursing homes need to have plans in place in the event of a cluster including pre-established access

Table 3

Univariate analysis of risk factors for development of acute respiratory disease and fatal outcome, nursing home B, Germany, 11–19 January 2009 (n=19)

	Disease OR (95% CI)	Fatal outcome OR (95% CI)
Age ≥90 years	2.1 (0.4–11.0)	3.0 (0.3–88.3)
Disorientated	2.0 (0.4–10.7)	5.3 (0.5–157)
Incontinence	1.4 (0.2, 12.6)	18.5 (1.6–633.6)
High level of care	0.7 (0.1, 3.9)	4.0 (0.4–117.7)
Not able to walk	2.3 (0.2, 65.6)	2.6 (0.2–32.5)
Low Braden Score	1.4 (0.2–12.6)	18.5 (1.6–633.6)
Influenza vaccination	0.7 (0.1–3.7)	2.2 (0.3–22.8)

CI: confidence interval; OR: odds ratio.

to rapid laboratory testing for aetiological agents causing respiratory and gastrointestinal infections as well as structures enabling them to quickly initiate appropriate antimicrobial therapies and infection control measures [24]. Identifying pathogens for gastrointestinal disease is important as some pathogens may require modification of hygienic standards such as improved environmental cleaning in the case of *C. difficile*, the change of antiseptic hand rub in the case of norovirus or specific medical treatment [17]. Furthermore, knowing the aetiological agent will direct the search for the source of an outbreak.

Control measures are most effective if initiated early during the course of an cluster [5,25] and early symptomatic treatment is crucial in the treatment of acute respiratory tract infection and severe gastrointestinal disease. Thus, active surveillance under real-time conditions is most desirable. As clusters in nursing homes can occur throughout the year, continuous vigilance is needed, but it may be of additional benefit to intensify surveillance during the winter months.

References

1. Strausbaugh LJ, Sukumar SR, Joseph CL. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. Clin Infect Dis. 2003;36(7):870-6.
2. Loeb M, McGeer A, McArthur M, Peeling RW, Petric M, Simor AE. Surveillance for outbreaks of respiratory tract infections in nursing homes. CMAJ. 2000;162(8):1133-7.
3. Mattner F, Sohr D, Heim A, Gastmeier P, Vennema H, Koopmans M. Risk groups for clinical complications of norovirus infections: an outbreak investigation. Clin Microbiol Infect. 2006;12(1):69-74.
4. Castle NG, Mor V. Hospitalization of nursing home residents: a review of the literature, 1980-1995. Med Care Res Rev. 1996;53(2):123-48.
5. Friesema IH, Vennema H, Heijne JC, de Jager CM, Morroy G, van den Kerkhof JH, et al. Norovirus outbreaks in nursing homes: the evaluation of infection control measures. Epidemiol Infect. 2009;137(12):1722-33.
6. Patriarca PA, Weber JA, Parker RA, Orenstein WA, Hall WN, Kendal AP, et al. Risk factors for outbreaks of influenza in nursing homes. A case-control study. Am J Epidemiol. 1986;124(1):114-9.
7. Vaux S, Poujol I, Bonmarin I, Levy-Bruhl D, Desenclos JC. Surveillance of lower respiratory tract infections outbreaks in nursing homes in France. Eur J Epidemiol. 2009;24(3):149-55.
8. Barker WH, Borisute H, Cox C. A study of the impact of influenza on the functional status of frail older people. Arch Intern Med. 1998;158(6):645-50.
9. Goodman RA, Orenstein WA, Munro TF, Smith SC, Sikes RK. Impact of influenza A in a nursing home. JAMA. 1982;247(10):1451-3.
10. Louie JK, Yagi S, Nelson FA, Kiang D, Glaser CA, Rosenberg J, et al. Rhinovirus outbreak in a long term care facility for elderly persons associated with unusually high mortality. Clin Infect Dis. 2005;41(2):262-5.
11. Falsey AR, Dallal GE, Formica MA, Andolina GG, Hamer DH, Leka LL, et al. Long-term care facilities: a cornucopia of viral pathogens. J Am Geriatr Soc. 2008;56(7):1281-5.
12. Fiore AE, Iverson C, Messmer T, Erdman D, Lett SM, Talkington DF, et al. Outbreak of pneumonia in a long-term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. J Am Geriatr Soc. 1998;46(9):1112-7.
13. Bennett RG. Diarrhea among residents of long-term care facilities. Infect Control Hosp Epidemiol. 1993;14(7):397-404.
14. Levine WC, Smart JF, Archer DL, Bean NH, Tauxe RV. Foodborne disease outbreaks in nursing homes, 1975 through 1987. JAMA. 1991;266(15):2105-9.
15. Lopman B, Vennema H, Kohli E, Pothier P, Sanchez A, Negredo A, et al. Increase in viral gastroenteritis outbreaks in Europe and epidemic spread of new norovirus variant. Lancet. 2004;363(9410):682-8.
16. Svraka S, Duizer E, Vennema H, de Bruin E, van der Veer B, Dorresteijn B, et al. Etiological role of viruses in outbreaks of acute gastroenteritis in The Netherlands from 1994 through 2005. J Clin Microbiol. 2007;45(5):1389-94.
17. Makris AT, Gelone S. Clostridium difficile in the long-term care setting. J Am Med Dir Assoc. 2007;8(5):290-9.
18. McGeer A, Campbell B, Emori TG, Hierholzer WJ, Jackson MM, Nicolle LE, et al. Definitions of infection for surveillance in long-term care facilities. Am J Infect Control. 1991;19(1):1-7.
19. Rothman KJ, Boice JD. Epidemiologic Analysis with a Programmable Calculator. Washington D.C.:United States Department of Health. 1979.
20. Martin D, Austin H. An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. Epidemiology. 1991;2(5):359-62.
21. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol. 2001;154(2):155-60.
22. Beck-Sague C, Jarvis WR, Martone WJ. Outbreak investigations. Infect Control Hosp Epidemiol. 1997;18(2):138-45.
23. Tamblyn SE. Recognizing and controlling respiratory disease outbreaks in long-term care facilities. CMAJ. 1997;157(9):1257-60.
24. Arden NH. Control of influenza in the long-term-care facility: a review of established approaches and newer options. Infect Control Hosp Epidemiol. 2000;21(1):59-64.
25. Monto AS, Rotthoff J, Teich E, Herlocher ML, Truscon R, Yen HL, et al. Detection and control of influenza outbreaks in well-vaccinated nursing home populations. Clin Infect Dis. 2004;39(4):459-64.

European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) 2011 – call for abstracts

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Citation style for this article:
Eurosurveillance editorial team. European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) 2011 – call for abstracts. Euro Surveill. 2011;16(22):pii=19882. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19882

Article published on 2 June 2011

The fifth European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) will take place in Stockholm, Sweden, from 6 to 8 November 2011.

As every year, ESCAIDE 2011 will draw together professionals from around the world to present and discuss developments in infectious disease epidemiology.

The call for abstracts for the conference is now open, and abstracts can be submitted via the dedicated 'call for abstracts' portal on the ESCAIDE website (http://www.escaide.eu/). The closing date for submissions is 8 July 2011.

The conference programme includes planned keynote sessions on:

- enhancing health and health equality through vaccination programmes
- the hospital as an infectious disease amplifier
- parasitic infections of increasing relevance for Europe
- infectious disease control in complex emergency situations.

Selected abstracts will be presented in oral sessions covering influenza, tuberculosis, HIV and other infectious diseases, and more general topics related to disease identification and intervention, including disease outbreak investigation methodology and outcomes, surveillance, antimicrobial resistance, vaccine preventable diseases and methods for microbial identification. Other accepted abstracts will be presented as posters.

The final programme details and conference registration instructions will be posted soon on the ESCAIDE website. It is expected that ESCAIDE 2011 participants can receive Continuing Medical Education (CME) credits for attending the conference.

For further information, contact:
escaide.conference@ecdc.europa.eu