Impact Factor 6.15

# Eurosurveillance

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

Vol. 17 | Weekly issue 30 | 26 July 2012

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# Re-emergence of brucellosis in cattle in France and risk for human health

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**Citation style for this article:**
Mailles A, Rautureau S, Le Horgne JM, Poignet-Leroux B, d'Arnoux C, Dennetière G, Faure M, Lavigne JP, Bru JP, Garin-Bastuji B. Re-emergence of brucellosis in cattle in France and risk for human health. Euro Surveill. 2012;17(30):pii=20227. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20227

Article submitted on 13 July 2012 / published on 26 July 2012

**A case of human brucellosis was diagnosed in France in January 2012. The investigation demonstrated that the case had been contaminated by raw milk cheese from a neighbouring dairy farm. As France has been officially free of bovine brucellosis since 2005, veterinary investigations are being conducted to determine the origin of the infection and avoid its spread among other herds. Hypotheses about the source of this infection are discussed.**

In January 2012, a human case of brucellosis was diagnosed by blood culture in a district of the French Alps. The isolated strain was identified as *Brucella melitensis* biovar 3. The patient had presented in late November 2011 with non-specific symptoms that had been ongoing since that date. Usual at-risk exposures were investigated: recent or ancient travel in an endemic/enzootic country, consumption of raw milk or raw milk products imported from an enzootic country, professional or accidental exposure to *Brucella* strains in a laboratory, direct contact with animals, etc. As the patient had not had such an exposure at any point before, the case was considered to be an autochthonous case of acute brucellosis of undetermined origin.

In April 2012, brucellosis was confirmed in a dairy cow in a herd of the same district of the French Alps. The seropositive cow had aborted in late January, and a strain of *Brucella melitensis* biovar 3 was isolated from the milk sampled from the animal. The animal belonged to a herd 21 dairy cows, and no other animal in the herd presented with symptoms suggesting brucellosis or showed any serological reaction. Approximately 20 kg of Reblochon cheese (soft raw milk cheese) are usually produced daily on the affected farm.

## Brucellosis surveillance in France

France has been officially free of brucellosis in cattle since 2005, and the last outbreak of brucellosis in sheep and goats was reported in 2003. In order to detect and prevent any re-emergence of the disease, annual screening using Rose Bengale test or complement fixation test is carried out in all cattle, sheep and goat farms producing raw milk as well as in all cattle herds, and every one to three years in small ruminant, according to EU regulations [1-4]. Moreover, abortion in ruminants is mandatorily notifiable and the investigation of abortion includes examination for brucellosis.

Human brucellosis in France is mandatorily notifiable. The National Reference Centre (NRC) determines the characteristics of *Brucella* strains isolated from patients [5,6]. Serological suspicions also have to be confirmed by the NRC, as the low specificity of available tests can be responsible for false-positive results. The confirmation is carried out using a combination of in-house tests including Rose Bengale test, immunoassay, complement fixation test, and specific detection of antibodies against *Yersinia enterocolitica*.

## Veterinary investigation

All animals were tested serologically (Rose Bengale test, complement fixation test and indirect enzyme linked immunosorbent assay) before slaughter in April [5]. Following French regulations, all animals in the infected herd were immediately slaughtered, and three pairs of lymph nodes (retro-pharyngeal, retro-mammary and internal iliac) were sampled from all animals for *Brucella* culture [5] and PCR [7]. All animals were seronegative with the exception of the index animal which showed a very strong reaction in all three tests. However, *Brucella* was isolated from a second animal in the herd, and PCR-positive results were obtained for

four further animals, in addition to the index animal and the second cow with an isolation of *Brucella*.

Following the confirmation of brucellosis in the cow, a trace-back investigation was implemented by the veterinary services to determine the origin of the contamination of the herd. The animals of the infected herd had not taken part in a transhumance nor did they graze with other herds on the same pastures. Other neighbouring farms as well as farms that had traded animals with the infected farm in the year before the outbreak were investigated. All tested negative in serology [5].

A trace-forward investigation was also carried out to determine the places of distribution of cheese produced at the affected farm since the abortion of the cow.

Reblochon cheese is a raw milk soft cheese, requiring a maturation period of three weeks to one month. The cheese from the affected farm had been commercialised after the abortion in seven districts. Cheese was sold directly at the farm, and as whole pieces or in parts in supermarkets. Cheese produced by the affected farm had not been exported to other countries but might have been bought by foreign tourists during their winter holidays in several ski resorts in the area. For this reason, the European rapid alert system for food and feed (RASFF) was informed.

## Human investigations

After the identification of the first bovine case, the human case was interviewed again to investigate any direct or indirect epidemiological link with the infected herd. During the second interview, it became clear that the patient and their family had visited the infected farm in autumn 2011, although it was not possible to determine the exact date. During this visit, the family had bought *Tome Blanche* cheese, a fresh cheese obtained during the first step of Reblochon production. The four family members had shared the *Tome Blanche* on the same day, but the index case was the only one who later presented with symptoms. The other three family members were serologically investigated in May 2012 and only one presented with a positive high titre in agglutination (1,600). The farm reported no other visitors during that period, apart from neighbours.

## Microbiological investigations

The strain isolated from the human case and from the two cows both belonged to *Brucella melitensis* biovar 3. The strains had the same genotype as determined by multilocus variable number tandem repeat analysis (MLVA) [8].

## Control measures

All cheese pieces produced by the affected farm and still within the shelf life were withdrawn from retailers. In addition, a recall of already sold products was carried out via a national press release by the cheese producer and by posters in the sale points. Medical doctors in the concerned districts were informed by the regional health authorities. Consumers of these products were advised to seek medical attention should they present symptoms consistent with brucellosis.

The release of cheese from the affected farm was immediately stopped. The movements of animals from other herds that had epidemiological links with the infected herd (those that were geographically close to the infected herd, or had been bought from the infected herd) have been restricted until the end of the investigation. Furthermore, raw cheese products from farms with epidemiological links to the infected farm were put on sale only after negative bacteriological tests results had been obtained.

## Reinforcement of human surveillance

Notification of human brucellosis is mandatory in France. All notified human cases in France have to be confirmed by the national reference laboratory. From 2002 to 2011, 219 human cases were confirmed in France. Among them, 183 (84%) were patients infected through the consumption of raw milk products or direct contact with animals in (or from) countries with enzootic brucellosis, 14 (6%) were laboratory workers infected through the handling of *Brucella* strains, 17 (8%) were relapses in people with past infection, while the origin of contamination could not be determined for five patients (2%) [9].

Because the investigation of the origin of the human case diagnosed in January 2012 had been inconclusive, it was decided to reinforce the surveillance immediately. Since January 2012, all notified suspected cases have been interviewed with a trawling questionnaire before the diagnosis was confirmed. Since April 2012, any epidemiological link with the infected herd has been systematically investigated. No other related human cases have been identified so far.

## Discussion

At this time, several hypotheses can be proposed to explain the re-emergence of brucellosis in cattle in France. One explanation is contact with an infected cattle or small ruminant. Knowing that the affected herd had not received any imported animals, it needs to be investigated whether animals had been introduced in one of the herds that sold animals to the affected farm or whether the affected herd had been in contact with animals of neighbouring farms. Another hypothesis would be a contamination of cattle by wildlife. Some chamois (*Rupicapra rupicapra*) were found infected with *B. melitensis* biovar 3 in 1988 in the Alps, and some of these animals may have become chronically infected and not display symptoms [10]. However, no infected chamois has been identified in the last 10 years, despite several serological surveys (Garin-Bastuji, personal communication, July 2012). *B. melitensis* biovar 3 is the most common biovar isolated in ruminants worldwide, and therefore the identification of this biovar in a district like the French Alps

with many different ruminant species cannot contribute to a more precise hypothesis.

The veterinary investigations are still ongoing to determine the origin of the contamination of the herd, to investigate the possible spread of the infection to other herds and to take control measures to avoid the infection of new herds and consequently the occurrence of additional human cases.

However, the absence of infected animals in the herds that are epidemiologically linked with the infected herd, and the absence of other autochthonous human cases argue in favour of a single outbreak and a limited episode. The index animal on the farm was born from a dam that itself was born in 1999 before the last outbreak in the area and died in 2006. The lifetime of the mother of the index infected animal is therefore consistent with the hypothesis of a congenital case of bovine brucellosis [11].

In addition to the investigations already carried out, all herds coming back from transhumance in the concerned district will be serologically screened during the fall. Serological tests lack specificity but they have a good sensitivity and are of good value to detect recent or active infections. The index animal had an active infection demonstrated by *Brucella* excretion in milk. This animal displayed a high level of antibodies in relation with the active although possibly chronic infection. During the early investigation, a *Brucella* strain and *Brucella* DNA were detected in ganglions of seronegative animals, demonstrating chronic latent infections, with no antibodies. Strengthened surveillance of human and animal brucellosis will be maintained until the end of the investigations.

The surveillance of human brucellosis in non-endemic countries is complicated by the lack of specificity of serological tests [12-16]. In our experience, all available tests still may cross-react with other bacteria (mainly *Y. enterocolitica*, but not only), and can also give false positive results in patients presenting with immune disorders. In countries with low prevalence and incidence of the disease, this low specificity contributes to the low positive predictive value of serology. A positive diagnosis has important consequences for the patients (long antimicrobial therapy with possible adverse effects and ecological consequences on intestinal bacteria), and for the dairy animals (culling of the entire herd in our country). It is therefore important to obtain as much evidence as possible to confirm a serological diagnosis.

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# Differences in hepatitis B infection rate between ethnic groups in antenatal women in Birmingham, United Kingdom, May 2004 to December 2008

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**Citation style for this article:**
Caley M, Fowler T, Greatrex S, Wood A. Differences in hepatitis B infection rate between ethnic groups in antenatal women in Birmingham, United Kingdom, May 2004 to December 2008 . Euro Surveill. 2012;17(30):pii=20228. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20228

Article submitted on 11 November 2011 / published on 26 July 2012

**Hepatitis B virus (HBV) is a major cause of morbidity and mortality worldwide. Although the United Kingdom (UK) prevalence of HBV is low, it is increasing. There is some evidence that the rate of infection is much higher in some populations living in Britain of non-white ethnicity or who were not born in Britain, compared with the British-born white population. We examined the prevalence of HBV infection in pregnant women through hepatitis B surface antigen (HBsAg) or e-antigen (HBeAg) in Birmingham UK between May 2004 and December 2008 and the effect of ethnicity on the relative risk of infection. There was a significant increase in the number of antenatal HBV infections detected over the study period from 106 cases in 2005 to 161 cases in 2008 (p=0.037). Women who define themselves as of black African, non-British white and Pakistani ethnicity had a markedly elevated rate of HBV infection (relative risk (RR): 11.25, 5.87 and 2.33 respectively) compared to the England average. Health organisations that serve populations with a high or increasing proportion of women originating from intermediate and high HBV prevalence areas of the world such as Africa, some parts of Europe and Asia, should anticipate a need for perinatal and postnatal prophylaxis to children born to HBV infected mothers.**

## Introduction

Hepatitis B virus (HBV) is a major cause of morbidity and mortality worldwide. It is estimated to have affected two billion people, 350 million of which have chronic infection [1]. The overall United Kingdom (UK) prevalence of chronic infection is low (<1%) particularly in pregnant women, however the annual number of hepatitis B notifications in England and Wales is increasing [1,2]. Although data on the prevalence of hepatitis B in the UK and the impact of migration patterns are limited, there is some evidence that the rate of infection is much higher in people not born in Britain or of non-white ethnicity compared with the British-born white population reflecting the higher HBV prevalence in their countries of birth or family origin [3,4].

All pregnant women in the UK are offered HBV testing as part of the national antenatal screening programme for infectious diseases. Women are offered HBV testing at their first antenatal appointment, usually at 8–12 weeks of pregnancy.

In the UK, pregnant women with HBV infection are treated based upon the severity of disease, and benefits of reducing viral activity balanced against potential side effects and the unknown teratogenicity of antiviral treatment [5]. These judgements are made by specialist physicians on a case-by-case basis. Vertical transmission of HBV infection occurs in 90% of pregnancies where the mother is hepatitis B e-antigen (HBeAg) positive and in about 10% of pregnancies where the mother is hepatitis B surface antigen (HBsAg) positive, e-antigen negative. More than 90% of infected infants become chronic carriers [6]. In the UK, babies born to HBV infected mothers should all receive a course of HBV immunisation starting with a first dose of vaccine at birth and three further doses at one, two and twelve months of age. Babies born to highly infectious mothers, this includes those who are positive for HBeAg, also receive hepatitis B immunoglobulin at birth. This regime reduces vertical transmission by 90% [1]. A booster vaccine at around five years of age is also recommended for those at ongoing risk.

The England average rate of HBV infection in antenatal blood specimens is 350 per 100,000 specimens [7]. Factors that influence prevalence include geographical location of residence and country of birth, with both people residing in urban areas and people born in countries of high prevalence having higher rates of infection [1,7].

The World Health Organization (WHO) has categorised countries based upon the prevalence of HBsAg into high (more than 8%), intermediate (2 to 8%) and low (less than 2%) prevalence countries [1]. The highest rates of HBV infection in low prevalence countries are often in people who immigrate from high prevalence countries [8,9]. However those groups at highest risk often have a lower uptake of preventative health services due to language barriers and a lack of awareness [10,11]. In immigrants from high prevalence to low prevalence countries, difficulties in mastering the language of the host country has also been found to correlate with poor levels of antenatal care [12]. It is therefore important that antenatal services meet the need of pregnant women infected with HBV and that services adapt as the demographics of the population they serve changes. This paper describes the differences in epidemiology of HBV infection in pregnant women in a large multiethnic city in England.

## Methods

Birmingham is the second largest city in the UK with a population of approximately 1.1 million. Based on 2001 UK census data, where ethnicity is self reported, and other factors affecting population change, it is estimated that 65% of the population are white British, 20% are of South Asian ethnicity and about 5% are from black ethnic groups. Solihull is a neighbouring metropolitan borough that is continuous with Birmingham and has a population of about 220,000. The Birmingham and Solihull Health Protection Unit receives all notifications of women testing positive for HBsAg or HBeAg as part of antenatal screening, who live within the boundary of the Birmingham and Solihull area.

All pregnant women between May 2004 and December 2008 who tested positive for HBsAg or HBeAg were identified as cases in this study. All cases were tested for HBsAg. In the vast majority of patients, HBeAg was tested, although a small number failed to have this test completed. Demographic details were recorded for all cases. Women who were identified as testing positive for HBV by antenatal screening in the time of this study, but who were previously known to have been diagnosed with HBV, were also included in the study. Where women were identified in two or more separate pregnancies during the study period, all pregnancies were included to estimate the level of demand for prevention and treatment services. Repeat pregnancies were excluded from ethnic group rate of infection and relative risk of infection calculations, in order to avoid counting the same cases more than once. Duplicate cases were removed manually. Regression analysis was used to examine the changes over time of the total number of cases per quarter. Differences between the rate of HBV infection in different ethnic groups were also examined using a chi-squared test.

Ethnicity was self reported by cases, choosing from a predefined list of ethnicity categories. This is the recommended method for identifying ethnicity by the Office for National Statistics (ONS) [13]. Ethnic categories were based on the 2001 census categories [13], but a number of categories were combined to allow meaningful comparisons. Membership of an ethnic category is not defined by place of birth, though this may be a determining factor in peoples' choice of group, but rather the ethnic group a person feels they belong to. Thus a person defining themselves as of black African ethnicity could be born in Africa or born in Britain but be a member of the black African community. The ethnicity categories comprised: (i) 'white British', denoting a person of white ethnicity who considers their ethnic background to be predominantly of British origin, (ii) 'white other', a person of white ethnicity who considers their ethnic origin from a country other than Britain, including the category 'white Irish', (iii) 'black African', (iv) 'black Caribbean', (v) 'black other', a person of black ethnicity who considers their ethnic origin not to be in Africa or Caribbean, (vi) Pakistani, (vii) Chinese, (viii) Bangladeshi, (ix) Indian, (x) 'Asian other', a person of Asian ethnicity who considers their ethnic origin to be from that of a country other than the countries listed above. Ethnicity data was collected using the primary ethnicity identified by the case. There was no capacity to capture dual ethnicity categorisation, and country of birth was not collected.

Denominator data on the ethnicity of all pregnant women was only available for the years 2007 and 2008. The categorisation of ethnicity differed slightly between the HBV infected cases and the denominator data because this information was collected by different organisations. Case data was collected by a questionnaire on epidemiology, which provided a more detailed breakdown of ethnicity, whilst denominator data was collected routinely by maternity services using broader categories as part of usual care. Therefore to calculate the rate of infection in different ethnic groups, it was necessary to merge some ethnicity categories with others. For these purpose the cases with ethnicity categories Chinese, 'black other', 'Asian other' and 'not stated' were merged into the 'other' category. Where denominator data was not required to calculate results, we used the entire dataset (May 2004–December 2008). Where denominator was required, for example to calculate the rate of infection in different ethnic groups, the dataset is restricted to cases in 2007 and 2008 only. Confidence intervals were calculated using standard methods [14].

## Results

Between May 2004 and December 2008, testing for antenatal screening for HbsAg and HbeAg revealed 595 cases with HBV infection. Of these cases 130/595 (22%) were previously known to be infected prior to their pregnancy. Of the 130 known cases, 108 had been diagnosed in a previous pregnancy within the study period. The majority, 347/595 (58%), of cases were in the 25–34 years-old age groups (Table 1). A total of 407

**TABLE 1**

Number of Birmingham residents diagnosed with hepatitis B on antenatal screening by age group, United Kingdom, May 2004–December 2008 (n=595)

| Age group in years | Number of hepatitis B cases |
|---|---|
| <20 | 14 |
| 20–24 | 105 |
| 25–29 | 181 |
| 30–34 | 166 |
| 35–39 | 100 |
| 40–44 | 27 |
| 45–49 | 1 |
| >50 | 1 |
| Total | 595 |

**TABLE 2**

Cases of hepatitis B diagnosed on antenatal screening, by ethnic group, Birmingham, United Kingdom, May 2004–December 2008 (n=595)

| Ethnic group | Number of cases | Percentage (%) of cases (95% confidence intervals) |
|---|---|---|
| Black African | 194 | 32.6 (28.8–36.4) |
| Pakistani | 146 | 24.5 (21.1–28.0) |
| Chinese | 67 | 11.3 (8.7–13.8) |
| Other[a] | 51 | 8.6 (6.3–10.8) |
| White other[b] | 31 | 5.2 (3.4–7.0) |
| Black other[c] | 25 | 4.2 (2.6–5.8) |
| Bangladeshi | 23 | 3.9 (2.3–5.4) |
| Black Carribean | 17 | 2.9 (1.5–4.2) |
| Indian | 16 | 2.7 (1.4–4.0) |
| Asian other[d] | 13 | 2.2 (1.0–3.4) |
| Not stated | 8 | 1.3 (0.4–2.3) |
| Not recorded | 3 | 0.5 (0.0–1.1) |
| White British | 1 | 0.2 (0.0–0.5) |

[a] Other ethnic group than listed in the table.
[b] White other than white British.
[c] Black other than black African and black Caribbean.
[d] Asian other than Bangladeshi, Indian, Chinese and Pakistani.

of 595 cases (68%) were in 'black African', Pakistani and Chinese ethnic groups (Table 2).

Regression analysis showed that there was a significant increase in the number of cases of hepatitis B being identified though antenatal screening from 106 cases in 2005 to 161 cases in 2008 (p=0.037) (Table 3). This represents a 52% increase in cases in 2008 compared to 2005 with an average increase of 13.7 cases per year. The effect of ethnicity was also examined and although the number of cases in different ethnic groups was significantly different (p<0.001) the rate of change in the number of cases over time between ethnic groups was not.

HBeAg status was available on 585 of 595 cases. Patients with a positive HBeAg test have the highest infectivity and are most likely to transmit the virus to their child. A total of 67 of 585 (11%) of cases were positive for HBeAg. Of HBeAg positive cases, 42 of 67 (63%) were in women of Chinese and Pakistani ethnicity (Table 4). Women with HBV infection of Chinese and Pakistani ethnicity were significantly more likely than other ethnicities to be HBeAg positive (chi-squared test p value<0.001 and 0.025 respectively).

Rates and relative risks of infection were only calculated for cases in 2007 and 2008. In the two latter years, excluding cases occurring more than once due to repeated pregnancies resulted in a total of 268 cases of HBV infection. Women of 'black African', Pakistani, 'white other' and 'other' ethnicities all had a significantly higher rate of infection when compared to the England average rate of 350 per 100,000 antenatal tests (Table 5). Women of 'black African' and 'white other' ethnicity had markedly elevated risks (relative risk (RR): 11.25 and 5.87 respectively) compared to the England average. Women of 'white British' ethnicity had significantly lower relative risks of infection (RR: 0.01) but this represents a single case and this result should be interpreted with caution.

**TABLE 3**

Total number of hepatitis B cases identified by antenatal screening per year and percentage of total annual cases by ethnic group, Birmingham, United Kingdom, May 2004–December 2008 (n=595)

| Year | Cases | Percentage (%) of total annual antenatal hepatitis B cases | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Black African | Pakistani | Chinese | Other | White Other | Other Black | Bangladeshi | Black Caribbean | Indian | Asian Other | Not stated | Not Recorded | White British |
| 2004[a] | 69 | 23 | 30 | 12 | 7 | 0 | 9 | 6 | 4 | 3 | 1 | 4 | 0 | 0 |
| 2005 | 106 | 36 | 31 | 5 | 5 | 5 | 5 | 5 | 4 | 3 | 2 | 1 | 0 | 0 |
| 2006 | 131 | 32 | 21 | 14 | 8 | 8 | 7 | 2 | 2 | 2 | 2 | 1 | 0 | 1 |
| 2007 | 128 | 38 | 27 | 9 | 9 | 7 | 3 | 3 | 2 | 3 | 0 | 0 | 0 | 0 |
| 2008 | 161 | 31 | 19 | 16 | 12 | 4 | 1 | 4 | 2 | 2 | 4 | 2 | 2 | 0 |

[a] The year 2004 does not represent data for a complete year, as data were only collected from May to December 2004.

**TABLE 4**

Cases of hepatitis B virus infection, by hepatitis B e-antigen status and ethnic group, Birmingham, United Kingdom, May 2004–December 2008 (n=595)

| | HBeAg negative | HBeAg positive | Not recorded | Total | HBeAg positivity rate (%) |
|---|---|---|---|---|---|
| Chinese | 48 | 17 | 2 | 67 | 25[a] |
| Black Caribbean | 13 | 4 | 0 | 17 | 24 |
| Pakistani | 117 | 25 | 4 | 146 | 17[a] |
| Other | 43 | 8 | 0 | 51 | 16 |
| Asian other[b] | 11 | 2 | 0 | 13 | 15 |
| Black other[c] | 22 | 3 | 0 | 25 | 12 |
| White other[d] | 29 | 2 | 0 | 31 | 6 |
| Bangladeshi | 21 | 1 | 1 | 23 | 4 |
| Black African | 186 | 5 | 3 | 194 | 3 |
| Indian | 16 | 0 | 0 | 16 | 0 |
| Not stated | 8 | 0 | 0 | 8 | 0 |
| Not recorded | 3 | 0 | 0 | 3 | 0 |
| White British | 1 | 0 | 0 | 1 | 0 |
| Total | 518 | 67 | 10 | 595 | 11 |

HBeAg: hepatitis B e-antigen.

[a] Significantly higher positivity than average, chi-squared p<0.05.

[b] Asian other than Bangladeshi, Indian, Chinese and Pakistani.

[c] Black other than black African and black Caribbean.

[d] White other than white British.

## Discussion

The number of cases of hepatitis B diagnosed through antenatal screening in Birmingham and Solihull increased over the period 2004–2008. However, as limited historical denominator information is available it is impossible to distinguish whether this increase is due to increased numbers of women attending antenatal screening from high risk groups or whether this represents an actual increase in the prevalence of infection.

The greatest burden of HBV infection in pregnant women cared for in Birmingham and Solihull is in women of 'black African', 'white other' and Pakistani ethnicity. Of these ethnicity categories, the rate of infection is greatest in 'black African' women at 3,938 per 100,000 or approximately 4%. This is a similar figure compared to estimates of HBV prevalence in intermediate prevalence countries [15]. It is also relatively consistent with a study in Liverpool, England that found the prevalence of HBsAg in people aged 20–44 years-old and born in Somalia to be 9.4% [16]. Having considered what is known about migration patterns in Birmingham, we hypothesise that the high rate of infection in women of 'white other' at 2,054 per 100,000, approximately 2%, reflects infection in recent immigrants from Eastern Europe where HBV prevalence is of the order of 2–7% [15]. However, more accurate information about nationality or country of birth is required to confirm this hypothesis.

In the 'other' ethnicity category, which accounted for a rate of infection of 671 per 100,000, 48% were of Chinese ethnicity. We hypothesise that the HBV infection rate in Chinese women may be substantially higher than estimated, due to the relatively small Chinese population in Birmingham and Solihull. However, the lack of denominator data for this ethnicity category limited our ability to analyse this directly.

The higher burden of HBeAg positivity in Chinese and Pakistani women suggests that clinicians should be particularly aware of the higher risks of vertical transmission in these groups and the greater likelihood of the need for neonatal immunoglobulin treatment.

Currently, screening for hepatitis B infection only occurs as part of antenatal infectious disease screening in order to reduce the mother to child transmission of HBV infection. Health services in areas with large 'black African', 'white other' and Pakistani populations may wish to consider introducing targeted testing/case finding for HBV in people from these ethnic groups, for example as part of new patient assessments at general practices. Wider testing of these high risk groups is important as antenatal screening misses the larger proportion of the population made up of non-pregnant women and men. Current guidelines for pre-exposure HBV vaccination do not include recommendations for vaccination based on ethnicity or being born in a country with a high HBV prevalence [1]. It is recommended, however, that some people travelling to high

**TABLE 5**

Ethnic group rate and relative risk, compared to the England average, of antenatal hepatitis B virus infection, United Kingdom, January 2007–December 2008 (n=268)

| Ethnic group | Rate of hepatitis B virus infections per 100,000 pregnant women (95% confidence interval) | Relative risk (95% confidence interval) |
|---|---|---|
| Reference[a] | 350 | Reference |
| White British | 3.9 (0.1–195.3)[b] | 0.01 (0.00–0.56)[b] |
| White other[c] | 2,054.2 (966.1–4,368.0)[b] | 5.87 (2.76–12.48)[b] |
| Indian | 411.1 (144.2–1,172.1) | 1.17 (0.42–3.35) |
| Pakistani | 815.1 (562.8–1,180.5)[b] | 2.33 (1.61–3.37)[b] |
| Bangladeshi | 641.0 (253.5–1,614.9) | 1.83 (0.73–4.61) |
| Black Caribbean | 557.9 (202.8–1,535.1) | 1.59 (0.58–4.39) |
| Black African | 3,938.4 (2,888.9–5,369.2)[b] | 11.25 (8.25–15.34)[b] |
| Other | 676.3 (363.9–1,256.9)[b] | 1.93 (1.04–3.59)[b] |

[a] England average [7].
[b] Significantly different at 0.05 level from the England average.
[c] White other than white British.

prevalence countries should receive vaccination prior to travel. The high prevalence rates amongst 'black African', 'white other' and Pakistani pregnant women found in this study provide a strong argument to reconsider targeted testing and immunisation for high risk ethnic groups. There is also evidence to show that selective vaccination of high risk groups with similar prevalence rates to groups identified in this study such as genitourinary medicine (GUM) clinic attendees, prisoners and dialysis patients is cost effective [17,18].

The most important limitation to this study is the lack of historical and linked ethnicity data for pregnant women. This prevented us from assessing trends over time to estimate the rate of increase in different ethnic groups. The ethnicity categories also differed slightly between the case data and the denominator data meaning that some ethnicity categories, notably Chinese, were merged with other categories in the final part of the analysis. We also did not have information on the country of birth for cases. This is likely to be a significant factor in determining the likelihood of HBV infection as the rate of infection for women of later generation immigrants is likely to approach that of the white British population, as is seen for many other infectious diseases, as opposed to recent immigrants who are more likely to carry the risk of the country they have moved from.

Despite these limitations, this study shows that the routine collection of ethnicity data can identify latent health inequalities that were previously unnoticed or only supported by anecdotal evidence. Healthcare organisations should continue to improve ethnicity recording to ensure that it is complete, accurate and consistent using nationally agreed categorisation.

Further research to corroborate these findings and quantify the burden of HBV infection in pregnant women of Chinese ethnicity is required as is research to examine the effect of country of birth on the rate of infection.

Organisations that serve populations with a high or increasing proportion of women originating from areas of the world with high prevalence of HBV infection should anticipate an increasing need for perinatal and postnatal prophylaxis to children born to infected mothers. This will be in addition to the increasing need for harm reduction measures and the treatment of patients with HBV infection and its sequelae. Healthcare providers should be particularly aware of the financial and human resource implications of an increasing rate of HBV infection in pregnant women which is likely to reflect the trend in the population as a whole.

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# Long-term control of vancomycin-resistant *Enterococcus faecium* at the scale of a large multihospital institution: a seven-year experience

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**Citation style for this article:**
Fournier S, Brossier F, Fortineau N, Gillaizeau F, Akpabie A, Aubry A, Barbut F, Chedhomme FX, Kassis-Chikhani N, Lucet JC, Robert J, Seytre D, Simon I, Vanjak D, Zahar JR, Brun-Buisson C, Jarlier V. Long-term control of vancomycin-resistant Enterococcus faecium at the scale of a large multihospital institution: a seven-year experience. Euro Surveill. 2012;17(30):pii=20229. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20229

Article submitted on 17 January 2012 / published on 26 July 2012

Repeated outbreaks of vancomycin-resistant *Enterococcus faecium* (VRE) occurred between 2004 and 2010 in Assistance Publique – Hôpitaux de Paris (AP-HP), a 23,000-bed multi-hospital institution. From August 2004 to December 2005, the French guidelines for preventing cross-transmission of multiresistant bacteria were applied. Because the number of VRE cases continued to increase, an institutional control programme was implemented from January 2006 onwards: It foresees stopping transfer of VRE and contact patients, separating VRE and contact patients in distinct cohorts, intervention of a central infection control team to support local teams, and quick application of measures as soon as first VRE cases are identified. Between August 2004 and December 2010, 45 VRE outbreaks occurred in 21 of the 38 AP-HP hospitals, comprising 533 cases. Time series analysis showed that the mean number of cases increased by 0.8 cases per month (95% confidence interval (CI): 0.3 to 1.3, p=0.001) before, and decreased by 0.7 cases per month after implementation of the programme (95% CI: -0.9 to -0.5, p<0.001), resulting in a significant trend change of -1.5 cases per month (95% CI: -2.1 to -0.9, p<0.001). The number of cases per outbreak was significantly lower after implementation of the programme. A sustained and coordinated strategy can control emerging bacteria at the level of a large regional multihospital institution.

## Introduction

Outbreaks of vancomycin-resistant *Enterococcus faecium* (VRE) occurring in hospitals represent a major problem in many countries [1]. The documented transfer of vancomycin resistance to methicillin-resistant *Staphylococcus aureus* (MRSA) strains is an additional reason for controlling the spread of VRE [2], especially in countries such as France where MRSA rates are high [3]. VRE have become endemic in the United States despite introduction in 1995 of national guidelines by the Centers for Disease Control and Prevention [4,5]. In France, the rate of asymptomatic VRE carriage at hospital admission was 0.3% in a national study conducted in 2006, showing that VRE are not endemic in the general population [6]. However, several VRE outbreaks have been reported in French hospitals during the last few years [7-9]. One of these outbreaks started in 2004 in one of the 38 hospitals of the Assistance Publique – Hôpitaux de Paris (AP-HP), the largest healthcare institution in France [7]. The present study describes the VRE infection control programme that allowed controlling the outbreaks that emerged between 2004 and 2010 in this large multihospital institution that serves 11.6 million inhabitants.

## Methods

### Setting

The AP-HP is a public health institution that administers 38 teaching hospitals (23 acute care (AC) and 15 rehabilitation/long-term care (RLTC) hospitals). AP-HP has a total of 23,000 beds, representing 36% of all hospital beds in the Île de France region that encompasses the city of Paris, suburbs and surrounding counties, and counts 11.6 million inhabitants. AP-HP admits approximately 1 million inpatients per year. Administrators and medical committees manage AP-HP hospitals locally, but decisions on large investments and medical developments are taken by the central administration. A local infection control team is in charge of prevention and surveillance of nosocomial infections in each hospital, but actions of foremost importance for the whole institution, such as the multidrug-resistant bacteria control programme, are coordinated centrally by a multidisciplinary infection control team (one infectious disease physician, one bacteriologist, one epidemiologist and one nurse) [10]. Until August 2004, VRE cases were scarce in this institution where surveillance of multidrug-resistant bacteria (such as extended-spectrum beta-lactamase-producing enterobacteria, methicillin-resistant *Staphylococcus aureus* or VRE) has been implemented in the early 1990s [11].

### Case definitions

VRE infection was defined as any patient with a VRE isolated from a clinical specimen, VRE colonisation was defined as any patient with a VRE isolated from a rectal swab. A VRE case was defined as any infected or colonised patient. A contact patient was defined as any patient whose stay overlapped with the stay of a VRE case for at least one day in the same unit. An outbreak was defined as at least two VRE cases (i.e. one index case and at least one secondary case among the contact patients) occurring in a given hospital, with a clear epidemiological link (stay during the same period of time in the same unit) and involving the same VRE strain based on species, van gene, antibiotic susceptibility and pulsed-field gel electrophoresis (PFGE) pattern. During the follow-up of each outbreak, the occurrence of a new case sharing the same strain, as defined by the above criteria, was considered as part of the same outbreak if the time between the discharge of previous cases and the detection of the new case was less than three months.

### VRE control programme

Three consecutive periods were distinguished based on the VRE control measures. During period 1 (August 2004 to December 2005), referred to as the 'VRE emerging period', the French national guidelines for preventing cross-transmission of multidrug-resistant bacteria, designed mainly for curbing MRSA rates [1], were applied as follows: (i) barrier precautions around VRE cases, and (ii) identification of VRE carriers (screening) by culturing rectal swabs from contact patients present in the unit.

In period 2 (January 2006 to December 2007), referred to as the 'Intervention period, an institutional VRE programme was designed and coordinated by the AP-HP central infection control team in response to a steady increase in the monthly number of cases that had occurred during period 1. This programme emphasised rapid and stringent application of organisational procedures as soon as a first VRE case was identified, as well as the commitment of the hospital management. During this period, the programme included the two measures already applied in period 1, but also a bundle of seven new measures, as follows:

- rapid reporting of every new VRE case to the AP-HP central infection control team,
- stopping transfers of cases and contact patients to other units of the hospital or to any other hospitals,
- particular attention to daily cleaning of VRE patient environments with disinfectant,
- extended VRE screening of contact patients to those already discharged or transferred from the involved unit after identification of index case,
- maintained screening of all contact cases until the outbreak was considered controlled, i.e. after all VRE cases have been discharged and after a period of at least three months without a new case,
- identifying discharged VRE and contact patients in case of readmission,
- and cohorting patients in three distinct areas with dedicated nursing staff: 'VRE patients' section, the 'Contact patients' section and the 'VRE-free patients' section for newly admitted patients with no previous contact with VRE patients.

To stimulate the efforts made by the local infection control teams and administrators, the central infection control team followed the number of new cases, of new outbreaks, difficulties in programme implementation, and regularly disseminated results within hospitals and central administration. Moreover, the central infection control team visited the hospitals regularly to help the local teams in applying the VRE programme.

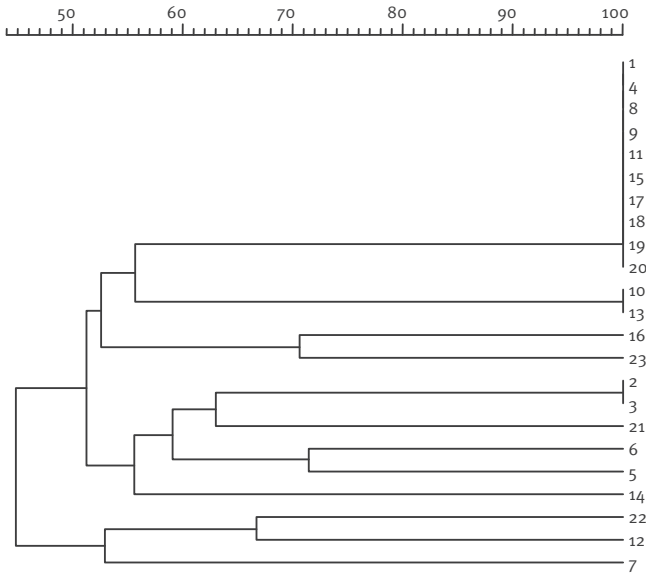
In period 3 (January 2008 to December 2010), referred to as 'Consolidation period', the VRE programme was routinely applied by local teams well trained on every aspect of the programme. The AP-HP central infection control team intervened only when local teams had difficulties in controlling outbreaks.

### Microbiological methods

Culture of rectal swabs was performed on selective media containing 6 mg/L vancomycin [12]. The API 20 Strep gallery (bioMérieux, Marcy L'Etoile, France) and GenoType *Enterococcus* assay (Hain Lifescience, Bandol, France) were used to confirm the identification of *E. faecium*. The latter genotypic method also allowed identification of which vancomycin resistance gene was involved (*vanA* or *vanB*) and was performed as early as possible at the local level or in an AP-HP

**Figure 1**

Dendrogram of vancomycin-resistant *Enterococcus* strains involved in hospital outbreaks, Assistance Publique–Hôpitaux de Paris, August 2004–December 2007 (n=23)

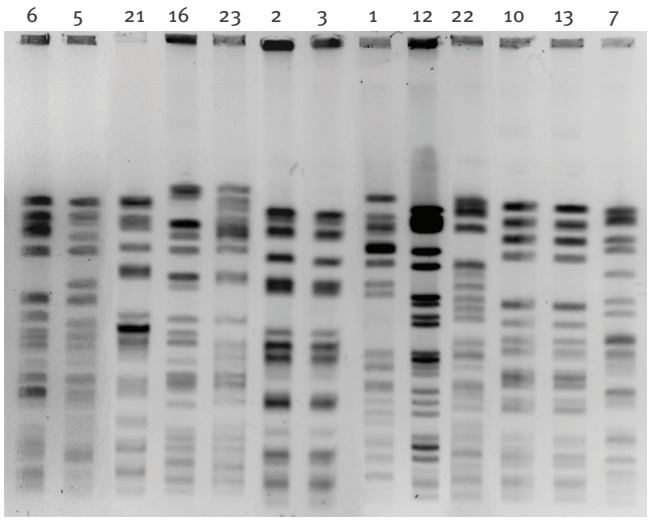



Produced by Dice analysis of the pulsed-field gel electrophoresis patterns and unweighed pair-group method with arithmetic averages. Percent similarities between strains are shown. Outbreaks are numbered in chronological order.

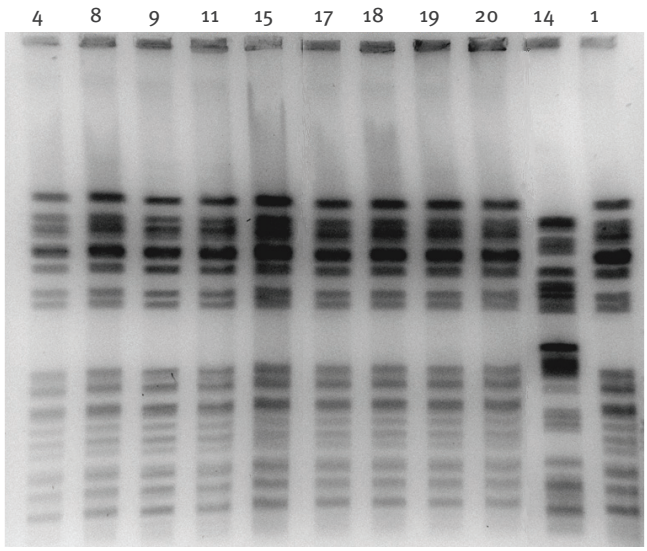
**Figure 2**

Pulsed-field gel electrophoresis patterns of vancomycin-resistant *Enterococcus* strains involved in hospital outbreaks, Assistance Publique–Hôpitaux de Paris, August 2004–December 2007 (n=23)

A




B




The strains sharing the same pattern (see Figure 1) are: 2 and 3; 10 and 13; 1, 4, 8, 9, 11, 15, 17, 18, 19, and 20.

laboratory nearby [13]. Isolates were tested for susceptibility to antibiotics by the agar disk diffusion method according to French guidelines [14]. Minimal inhibitory concentrations (MIC) of vancomycin and teicoplanin were measured using E-test (AB Biodisk, France).

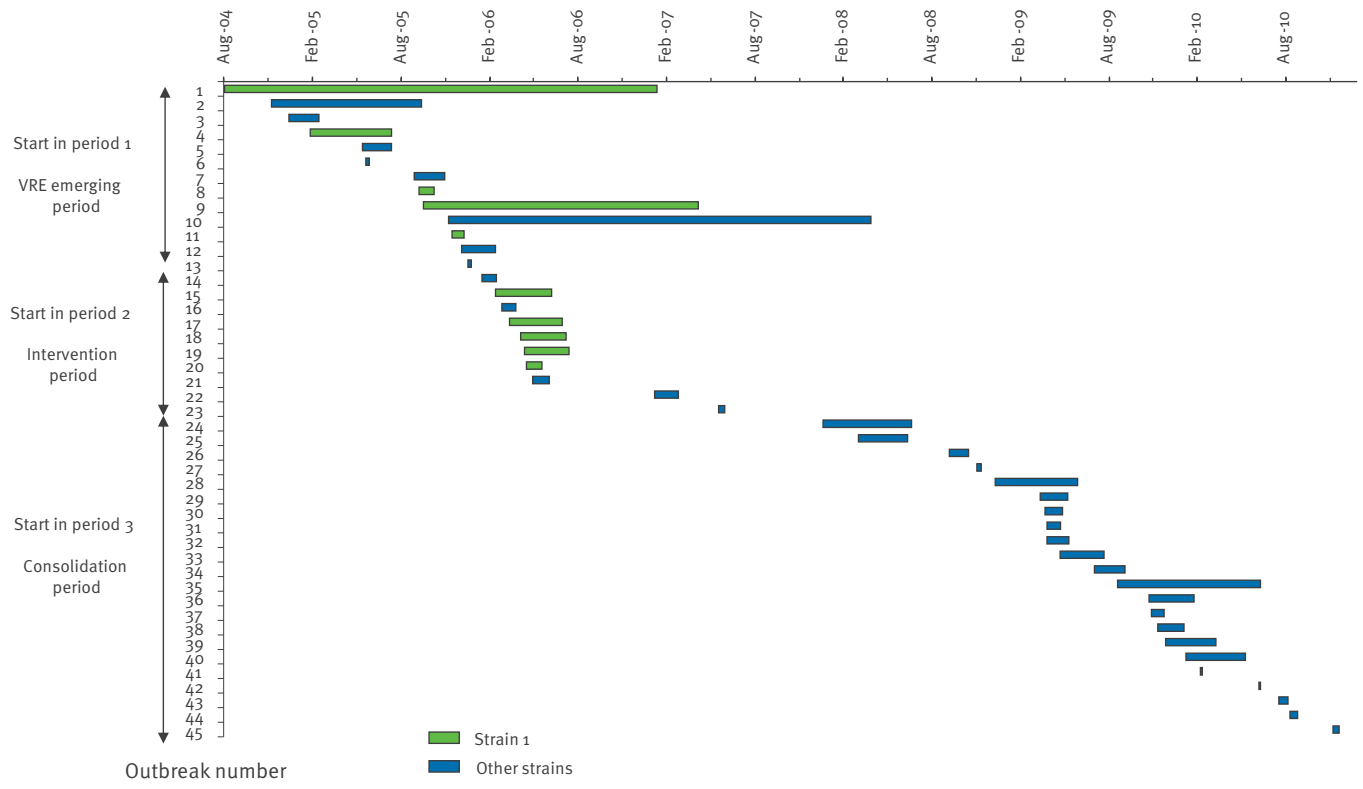
VRE strains isolated in each hospital were subjected to pulsed-field gel electrophoresis (PFGE) using a method by Murray et al. [15] that allows defining outbreaks, either in the local laboratory, or in a reference laboratory. Moreover, representative strains of each outbreak that occurred during periods 1 and 2 were collected centrally and subsequently compared by the same method. The Dice correlation coefficient was used to analyse the similarity of the PFGE banding patterns of SmaI-digested DNA. Clustering was based on the unweighed pair-group method with arithmetic averages (UPGMA). Finally, the PFGE patterns were interpreted using criteria from Tenover et al. [16] adapted by Morrison et al. [17].

## Statistical analysis

The evolution of the epidemic situation in the institution during the study was evaluated by analysing the monthly number of new VRE cases in all AP-HP hospitals. A segmented regression analysis of interrupted time series was conducted to assess the impact of the intervention after implementation of the VRE programme, both immediately and over time [18]. The model assumed a linear relationship between time and the number of new cases in each period, allowing for an abrupt change in level immediately after the start of the intervention and a change in the trend (estimated as the difference between pre-intervention and intervention slopes). From the model obtained in period 1,

**Figure 3**

Timeline of successive hospital outbreaks of vancomycin-resistant *Enterococcus*, Assistance Publique–Hôpitaux de Paris, August 2004–December 2010 (n=45)




Each outbreak is represented by a line indicating the time between the date of detection of the first and the last case. Outbreaks due to strain 1 are coloured in green. This figure shows the temporal overlap of the 10 outbreaks caused by this particular strain in eight distinct hospitals.

we calculated the expected monthly number of new cases during period 2 with 95% confidence intervals (CI). This method produces a simple representation of what would have happened if no further intervention had occurred and allows comparing expected with observed values.

The median number of cases in each outbreak was presented with its interquartile range (IQR) and compared between the three periods using the exact Wilcoxon test. We considered the month of detection of the outbreak to allocate them to each period.

All statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, North Carolina, United States). A p value ‹0.05 was considered statistically significant.

## Results

Between August 2004 and December 2010, 45 distinct VRE outbreaks occurred in 21 of the 38 AP-HP hospitals, (16 of the 23 AC hospitals, and five of the 15 RLTC hospitals). Eight hospitals experienced a single outbreak, whereas eight hospitals experienced two outbreaks, two hospitals three outbreaks, two hospitals four outbreaks and one hospital seven outbreaks. Most outbreaks occurred on intensive care (n=12), geriatrics (n=10), digestive surgery (n=6), and nephrology (n=5) wards.

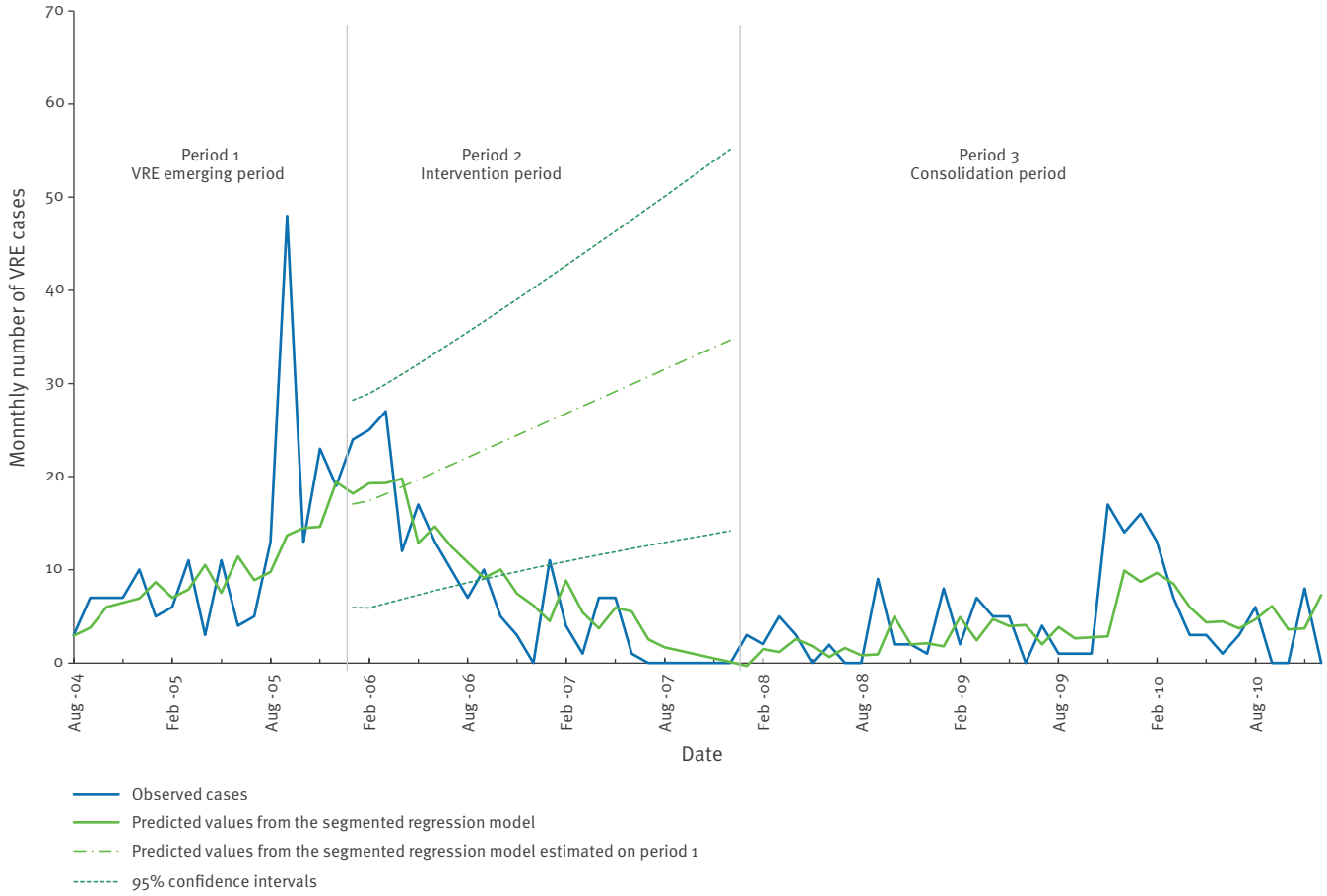
The 45 outbreaks comprised 533 cases, with a ratio of infected to colonised patients of 1:6. Most infections were urinary tract infections (51%), bacteraemias (15%) and peritoneal infections (13%).

The only species involved in these outbreaks was *E. faecium*. The gene encoding vancomycin resistance was *vanA* in 41 outbreaks and *vanB* in four outbreaks. Within each outbreak, the VRE strains shared the same PFGE pattern. PFGE patterns of the VRE strains involved in the 23 outbreaks that occurred in periods 1 and 2, allowed us to distinguish 12 distinct strains (Figures 1 and 2).

The strain involved in the first outbreak (112 cases), whose unusual antibiotic susceptibility pattern for a *vanA* genotype has been previously described [7], was also involved in nine other outbreaks affecting a total of eight distinct hospitals (Figures 1 and 2). The temporal overlap between the 10 outbreaks caused by this strain, as well as frequent links between the hospitals involved, strongly suggested inter-hospital dissemination (Figure 3).

**Figure 4**

Observed cases and predicted values of monthly vancomycin-resistant *Enterococcus* cases before and after implementation of the infection control programme, Assistance Publique–Hôpitaux de Paris, August 2004–December 2010 (n=533)




VRE: vancomycin-resistant *Enterococcus*.

## Comparisons between the three periods

Figure 4 shows the time series analysis of the monthly VRE cases from August 2004 to December 2010 and the predicted values from the segmented regression model (with a first-order autoregressive error) for period 1 (August 2004 to December 2005), period 2 (January 2006 to December 2007) and period 3 (January 2008 to December 2010), i.e. from before until after the implementation of the enhanced control measures. During period 1, the estimated number of VRE cases increased significantly by 0.8 cases per month (95% CI: 0.3 to 1.3, p=0.001) and was estimated at 2.9 in August 2004 and 19.4 in December 2005. During period 2, the number of VRE cases decreased by 0.7 cases per month (95% CI: -0.9 to -0.5, p<0.001) resulting in a significant trend change between the two periods of -1.5 cases per month (95% CI: -2.1 to -0.9, p<0.001). The estimated number of VRE cases decreased from 18.2 cases in January 2006 to 0.1 cases in December 2007. If no intervention had occurred, the number of VRE cases would have been expected to exceed 34 cases per month in period 2, and the predicted lower limit of the 95% CI forecast would have been greater than the observed number of VRE cases after November 2006 (see Figure 4 and the predicted values for period 2 if no intervention had occurred). In period 3, when the VRE programme was routinely applied by local teams, the number of index cases was a little higher than in period 2, particularly between April and December 2009, and one of the outbreaks was caused by delayed and incomplete implementation of bundle measures (see peak between November 2009 and February 2010 in Figure 4). Still, the number of observed cases remained markedly lower than the predicted lower limit of the 95% CI forecast.

If the mean number of new outbreaks of VRE per month did not decrease significantly over the three periods (0.8, 0.4 and 0.6 cases per month, respectively, in periods 1, 2 and 3), the median number of cases per outbreak was 9.0 (IQR: 4.0–37.0) in period 1 and 4.0 (IQR: 2.0–8.0) in periods 2 and 3, respectively (p=0.027).

## Discussion

This prospective multicenter study, carried out in the largest public multi-hospital institution in France,

assessed the positive impact of an institutional control programme on the evolution of VRE outbreaks. The main result of the programme was the progressive and significant decrease in the overall number of new VRE cases in the AP-HP hospitals in the Paris region in 2006–07 (Intervention period, period 2), i.e. after implementation of a specific control programme. This decrease contrasts with the continuing increase that prevailed in 2004–05 (VRE emerging period, period 1), when French guidelines aiming at controlling cross transmission of endemic multidrug-resistant bacteria such as MRSA were used. Most importantly, the progress made during the intervention period lasted during the following Consolidation period of three years (period 3). Moreover, the median number of cases per outbreak was significantly lower after implementation of the specific control programme.

Our study has potential limitations since it was not a randomised, controlled trial aiming at assessing causality between intervention and outcome. The rapid spread of VRE triggered quick and strong actions to control the phenomenon at the institutional level, making randomised intervention impossible. However, the fact that the strength and nature of the enhanced measures implemented in periods 2 and 3 differed markedly from those in period 1, as well as the length of the study and the number of points of measurements are a justification to consider this study as a quasi-experimental study with pre-test and post-test periods [19].

Vancomycin consumption remained unchanged from 2003 to 2010, around 12 defined daily doses per 1,000 days of hospitalisation, and thus could not have influenced the decline in VRE cases (data not shown).

Bundle measures similar to those implemented in period 2 and sustained in period 3 have been associated with control of VRE outbreaks in individual hospitals in areas where VRE are emerging and not yet endemic [9,20,21]. Our study suggests that such measures can suppress VRE emergence by controlling outbreaks at the level of a large institution that covers a region with more than 10 million inhabitants.

The results obtained with the VRE programme are due to the implementation of a bundle of new additional measures, more extensive than the barriers precautions used before, notably stopping transfer of VRE patients and cohorting patients with dedicated nursing staff. Since we implemented all parts of the bundle measures at the same time in period 2, it is not possible to delineate the respective impact of the individual activities. Stopping the transfer of VRE cases and the transfer of contact patients within and between hospitals was most likely crucial for decreasing VRE spread in our institution. Colonisation pressure, i.e. the number of colonised patients present in a given unit, has been found to be an important variable affecting VRE acquisition [22]. Cohorting patients with dedicated nursing staff in three different sections is advocated to minimise VRE cross-contamination [23]. Implementation of cohorting required a strong and sustained involvement of chief nurses and heads of departments, as well as of administrators. The financial implications of such measures have been discussed by Ridwan et al: dedicated nursing staff, costs of surveillance cultures and molecular typing, of gowns and disinfection procedures, loss of admissions [23].

Screening contact patients has been emphasised by several authors [5,20,21,24]. Indeed, it is known that VRE-colonised patients outnumber infected patients several-fold [24]. The ratio found in our study (6:1) is lower than in several other studies (from 7:1 to 20:1) [21,24]. Screening in our study was focused on identifiable contact patients, i.e. any patient whose stay overlapped with the stay of a VRE case for at least one day in the same unit; a larger screening strategy could explain the higher ratio reported elsewhere. A large majority (36/45) of the outbreaks reported in this present study included at least one clinical infection. The remaining nine contained only colonised cases and could have been designated as clusters of colonisations. Since faecal VRE carriage may persist for months or years, systematic identification of contact patients both of infected and colonised cases was important to quickly isolate them in case of re-admission [25].

A rapid and strong intervention at the beginning of an outbreak is probably crucial in limiting its size and duration. The sooner the index case and the first secondary cases are isolated and cohorted and contact patients are identified and screened, the lower is the risk of additional cross-transmissions. Our study shows that, although VRE index cases continue to happen in our region due to admission of carriers [6], and although some secondary cases can occur when the identification of the index case is delayed, the outbreaks can be quickly controlled and the number of secondary cases strongly limited. This requires quick and sustained mobilisation of all stakeholders, particularly the infection control team, medical and nursing staff, microbiologists and hospital administrators [9]. The strong commitment of the AP-HP institution, continuous coordination and support by the central infection control team, as well as a continuous feedback stimulated the efforts made in each hospital. In December 2006, the AP-HP programme was extended by the health authorities to cover all of France, and the rate of VRE in *E. faecium* was maintained at a very low level (0.8%) and even decreased in France between 2005 and 2009 as shown by the European Antimicrobial Resistance Surveillance Network [3].

The proactive strategy to control VRE can be also applied successfully in the control of carbapenemase-producing enterobacteria [26,27], another emerging multidrug-resistant bacterium, and should be promoted at the European level as suggested by several authors [23,28]. A sustained and coordinated strategy, set up in 1993 in our institution, has led to a

continuous decrease of MRSA rates, particularly since 2001 [10]. It is interesting to note that VRE began to spread in our institution in 2004 despite the MRSA programme, and was contained only when a specific VRE programme has been implemented. Such institutional programmes, based on a coordinated policy, are efficient ways to bring together and motivate hospital staff and managers, and to promote quality and safety in healthcare.


## Acknowledgments

We thank Hervé Blanchard, Michel Denis, Catherine Doit, Jean-Michel Guérin, Guillaume Kac, Christine Lawrence, Véronique Moulin, Martine Rouveau from the Assistance Publique - Hôpitaux de Paris infection control teams and Michèle Huang, Ségolène Neuville, Catherine Monteil, Roland Gonin and Jean-Marc Boulanger from central administration for their commitment in VRE outbreaks control. We are indebted to Antoine Andremont, Patrick Berche, Edouard Bingen, Jean-Louis Gaillard, Laurent Gutmann, Marie-Hélène Nicolas-Chanoine, Patrice Nordmann, Jean-Claude Petit, Bertrand Picard, Claire Poyart and Marie-José Sanson-Le Pors for organising the laboratory-based survey and VRE screening.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