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ORIGINAL ARTICLES

Outbreak report

PROLONGED OUTBREAK OF B MENINGOCOCCAL DISEASE IN THE SEINE-MARITIME DEPARTMENT, FRANCE, JANUARY 2003 TO JUNE 2005

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Between January 2003 and June 2005, an outbreak of meningococcal disease occured in the department of Seine-Maritime in northern France. Eighty six cases were notified, giving an average annual incidence of 2.7 cases per 100 000 inhabitants, compared with 1.6 in France. An especially affected area was defined as the city of Dieppe and its surrounding area (26 cases, giving an annual incidence of 12 cases per 100 000). This outbreak was due to *N. meningitidis* phenotype B:14:P1.7,16 belonging to the clonal complex ST-32/ET-5. Over the 31 B14:P1.7,16 cases confirmed by phenotyping methods at the national reference centre for meningococci (CNR, Centre National de Référence des méningocoques) the case-fatality rate (19%) and the proportion of purpura fulminans (42%) were especially high. Teenagers aged between 15 and 19 years and children aged 1 to 9 years were the most affected. In 2003, health authorities put in place enhanced epidemiological surveillance and informed practitioners and population about the disease. In 2004, the national vaccination advisory board studied the opportunity of using a non licensed outer membrane vesicle vaccine developed in Norway which may be effective against the B14:P1.7,16 strain. The Ministry of health decided in 2006 to offer vaccination with this vaccine to people aged 1 to 19 years in Seine- Maritime.

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Introduction

In France, invasive meningococcal disease (IMD) is a mandatory notifiable disease [1] and strains isolated from patients are sent to the national reference centre for meningococci (CNR, Centre National de Référence des méningocoques). The last evaluation of IMD surveillance estimated the exhaustivity of mandatory reporting at 80% [2,3]. The goal of the surveillance is rapid detection of clusters or abnormal situations

for prompt response and monitoring of national trends. The IMD incidence rate has been below 2 cases per 100 000 inhabitants for the past 10 years. Ninety seven percent of IMD cases are sporadic and IMD is associated with serogroup B in 59% of cases. Close contacts of IMD cases are offered chemoprophylaxis, and if appropriate, vaccination, as documented in the national guidance [4].

At the beginning of 2003 the national institute for public health surveillance (InVS, Institut de Veille Sanitaire) was alerted by the high incidence of serogroup B IMD cases in the north of the department of Seine-Maritime, Haute Normandy region, population 1 237 263. A similar increase had been observed in the same department in 1997, associated with high incidence of the B serogroup serotype 14 and serosubtype P1.7,16 belonging to the electrophoretic type 5 [5].

From 2003, health authorities set up an enhanced surveillance, collecting data on demographic, clinical, epidemiological and biological characteristics of each new cases and raised awareness of the disease among health practitioners aware and the general public.

This report describes the outbreak in Seine-Maritime, between 1 January 2003 and 30 June 2005.

Methods

Since 2002 the case definition of IMD has been a patient with Gram negative cocci in direct examination of cerebrospinal fluid (CSF) or *N. meningitidis* isolated from a sterile site; a patient with purulent CSF with presence of meningococcal antigens or positive polymerase chain reaction (PCR); or a patient with purpura fulminans or purulent CSF and purpuric spots.

For this outbreak, B:14:P1.7,16 cases were identified by culture or PCR from a sterile site. IMD cases included in the analysis were patients living, studying or working in Seine-Maritime and with dates of hospital admission between 1 January 2003 and 30 June 2005.

In the Seine-Maritime department we assumed that all cases were reported because of the enhanced surveillance and the high medical awareness during the outbreak. Specific care was taken to send samples to the CNR quickly.

To calculate incidence, each case was assigned to the department where the patient was normally resident. An especially affected area was defined by tracing a circle around the city of Dieppe including the homes of all the cases, and a total of 84 500 inhabitants. The P values for comparisons were estimated using the Fisher exact test or the chi-square test. Population estimates in 2003 were issued from the national office for demographic studies (INSEE) and from the 1999 census data for Dieppe area.

Results

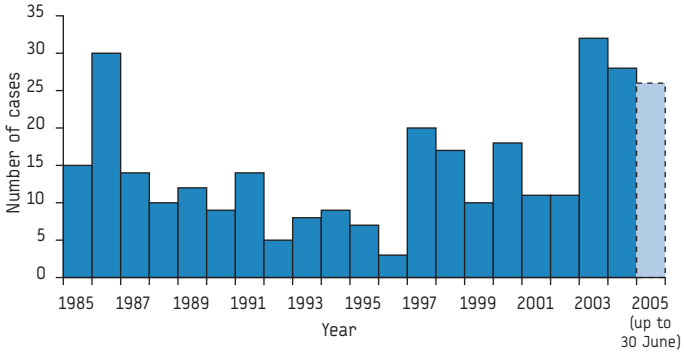
The outbreak in Seine-Maritime

From 1 January 2003 to 30 June 2005, 31 of the 86 IMD cases notified in the Seine-Maritime department were B:14:P1.7,16. The average annual incidence of IMD was 2.7 cases per 100 000 inhabitants. During the same period, the annual national incidence was 1.6 per 100 000 inhabitants (P=0.000). Since the 1997 rise associated with *N. meningitidis* B:14:P1.7,16 the number of IMD reported has remained high [FIGURE 1].

Of the 86 IMD cases, 32 were notified in 2003, 28 in 2004 and 26 between 1 January and 30 June 2005 [FIGURE 2]. In February 2005 a large peak of eight reported cases was observed. During the two first years the cases occurred mainly in the Dieppe area with 10 cases (incidence 11.8/100 000) in 2003 and 13 (incidence 15.4/100 000) in 2004. The incidences in the rest of the department were 1.9/100 000 (2003) and 1.3/100 000 (2004). In the first six months of 2005, 3 of the 26 cases were from the Dieppe area, with a six month incidence of 3.6/100 000 in the Dieppe area and 2.0/100 000 in the rest of the department. The situation was localized to the department of Seine-Maritime and none of the 6 surrounding departments presented an increase of IMD incidence rate during the study period.

FIGURE 1

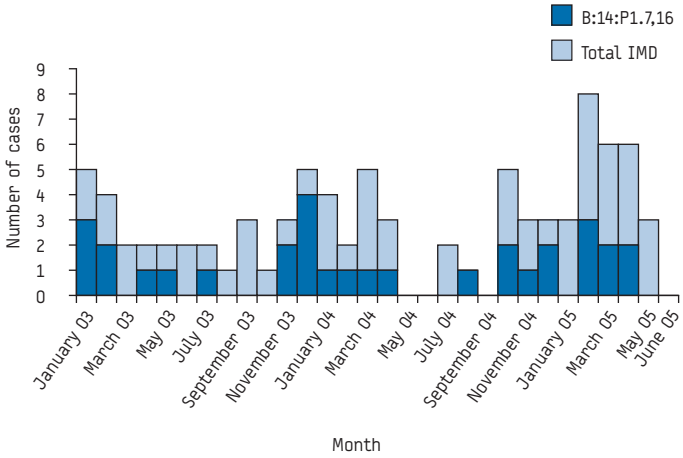
Number of invasive meningococcal disease cases notified, Seine Maritime department, January 1985 to June 2005



Note: Notification criteria were expanded in 2003 to include cases without microbiological confirmation. In 1997, a total of 31 cases were identified in the department but only 20 corresponded to the mandatory case definition at that time

FIGURE 2

Distribution of IMD cases reported by month, Seine Maritime department, France, January 2003 to June 2005



Of the 86 cases, 70 were laboratory confirmed: 61/70 (87%) were serogroup B, 8/70 (11%) were serogroup C and one (1%) was serogroup W135 or Y. Among the 61 serogroup B strains, 31 (50%) were B:14:P1.7,16, 15 (25%) could not be typed nor subtyped and 15 (25%) belonged to a variety of different types and subtypes.

The male:female ratio was 1.3 (48/38) compared with 1.0 in the whole of France (P=0.260). All age groups were affected with the highest age specific incidences observed among children less than 5 years and teenagers 15-19 years old [TABLE 1]. Teenagers accounted for 26% of the cases, compared with 18% in France (P=0.068).

TABLE 1

Number, percentage and averaged specific incidence of IMD, January 2003 - June 2005, Seine Maritime and France

Age in years	IMD cases		Annual specific incidence, Seine Maritime per 100 000	Annual incidence, France* per 100 000
	No.	%		
<1	6	7.0	18.3	17.3
1-4	18	20.9	13.7	5.5
5-9	10	11.6	5.0	1.1
10-14	9	10.5	4.1	1.3
15-19	22	25.6	9.6	4.5
20-25	7	8.1	3.4	2
≥25	14	16.3	0.7	0.5
Total	**86**	**100.0**	**2.8**	**1.45**

* Corrected for under-reporting

Of the 86 cases, 55 (64%) had septicaemia only or septicaemia associated with meningitis and 31 (36%) had meningitis only. *Purpura fulminans* was observed in 39 cases (45%), in a highest proportion than in France, 29% (P=0.000). During the study period 14 patients

died, giving a case fatality rate (CFR) of 16%. The CFR decreased over time from 25% (8/32) in 2003 to 14% in 2004 (4/28) and 8% (2/26) in the 6 first months of 2005. Two clusters occurred in the Dieppe area: one made up of two friends in the same village (co-primary cases, 1 identified B:14:P1.7,16), the other made up of two brothers (first case identified B:14:P1.7,16, the secondary case occurred within 48 hours although chemoprophylaxis had been given). A girl and her grandfather living in the city of Rouen also developed the disease within 48 hours of one another (the cases were B serosubtype P1.7,16).

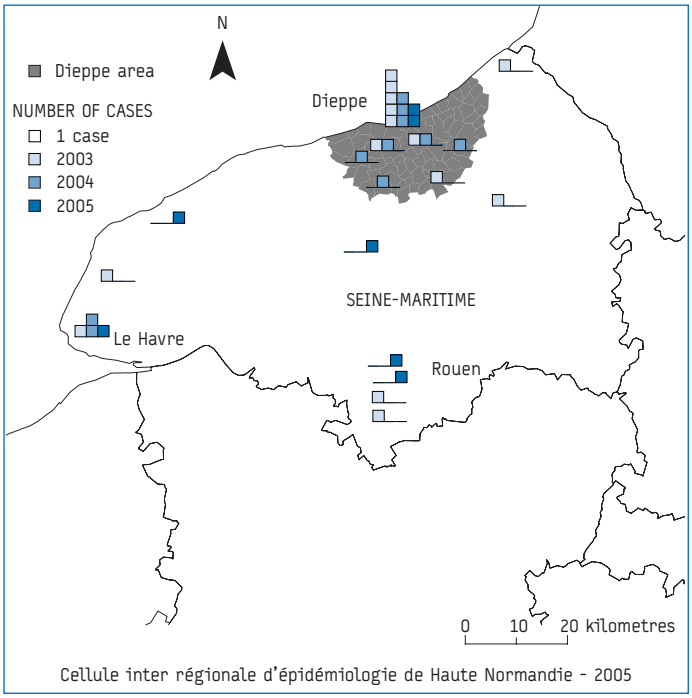
B:14:P1.7,16 confirmed cases

A total of 31 B:14:P1.7,16 cases were confirmed by phenotyping methods at the CNR, 14 in 2003, 10 in 2004 and 7 in the first six months of 2005. In 2003-2004, 16/24 cases (67%) occurred in residents of Dieppe area. Residents of this area make up 6.8% of the population of the Seine-Maritime department. From January to June 2005, among the 7 B:14:P1.7,16 cases, 2 occurred in Dieppe area [FIGURE 3].

The proportion of B:14:P1.7,16 cases varied by age group: 59% of all cases in teenagers (aged 15-19 years) were B:14:P1.7,16, but no B:14:P1.7,16 cases occurred in children aged under 1 year [TABLE 2]. The male:female ratio of B:14:P1.7,16 cases was 1.8 (20/11). In 2004-2005, the sex ratio tended towards 1.

FIGURE 3

Geographic distribution of B:14:P1.7,16 cases identified in Seine Maritime, by year, 1 January 2003 – 30 June 2005



Sources: InVS, NRC

Among the 31 B:14:P1.7,16 cases, the CFR was 19% (6 deaths) (serogroup B IMD CFR in France: 8%, P=0.031) and 42% (13) had purpura fulminans (B IMD national proportion: 24%, P=0.026).

During the study period, the CNR identified a total of 1493 invasive *N. meningitidis* samples in residents of France, of which 62 were invasive isolates of *N. meningitidis* of the phenotype B:14:P1.7,16 from a sterile site. Invasive isolates with phenotype B:14:P1.7,16 accounted for 4.2% of all strains and 7% of serogroup B strains. Twenty eight isolates (45%) of the phenotype B:14:P1.7,16 were from Seine-Maritime (differences with presented data are due to one patient residing outside the department and two cases classified B:14:P1.7,16 in our study because of the presence of clinical and biological signs of meningococcal infection and a B:14:P1.7,16 strain isolated from the pharynx but not taken into account by the CNR). Most of the other 34 invasive isolates were from neighbouring departments, where their presence was not associated with increase in incidence. Isolates from Seine-Maritime were further shown to belong to the clonal complex ST-32/ET-5. Strains with phenotype B:14:P1.7,16 were first isolated in France in 1989 in the Seine-Maritime department. They then appeared sporadically in other departments and were identified from a cluster in the eastern city of Metz in 2003 [6].

Control of the outbreak

Information meetings were organised by the local health authorities from 2004 for hospital physicians and other health professionals working out of hospitals (general practitioners, paediatricians…). Awareness of symptoms was promoted in the general public, with a document entitled *'Les infections invasives à méningocoque en Seine-Maritime : "repérer pour agir"'* that was widely distributed in December 2004, by items in print media articles and radio spots from 2003, and a television programme on the topic in January 2005. From January 2005, reports were produced on the InVS website, four times a year to begin with, changing to monthly. Three meetings with the local and national health authorities and the national experts were organised by the national board of health (DGS, Direction Générale de la Santé) and three telephone conferences were hold during the period. Several meetings of the national vaccination advisory board (CTV, Comité technique des vaccinations) were held in 2004 and 2005 to evaluate the risks and benefits of using an unlicensed outer membrane vesicle (OMV) vaccine developed against *N. meningitidis* phenotype B:15: P1.7,16 in Norway.

Discussion

In 2003, the incidence of IMD began to rise in Seine-Maritime because of the incidence in Dieppe area. Teenagers were more affected by the B:14:P1.7,16 strain than other age groups but 60% of the cases aged 5 to 9 years couldn't be grouped, typed or subtyped and may be therefore considered as possible B:14:P1.7,16. This might reflect different diagnosis practices or feasibility of isolating the strain in samples from this age group. In winter 2004-2005 and spring 2005, the outbreak seemed to spread in the rest of the department.

TABLE 2

Number and percentage of cases of IMD by age, Seine Maritime, France, January 2003 to June 2005

Age in years	B:14:P1.7,16	%	B without antigenic characterisation	%	Clinically diagnosed cases	%	Other confirmed cases	%
<1	0	0	1	7	1	6	3	13
1-4	6	33	4	27	4	25	5	21
5-9	3	30	1	7	4	25	2	8
10-14	4	44	3	20	0	0	2	8
15-19	13	59	3	20	3	19	3	13
20-25	1	14	1	7	2	13	3	13
≥25	4	29	2	13	2	13	6	26
Total	**31**		**15**		**16**		**24**	

The data presented suggest a local and persistent outbreak due to a particular strain. This situation was observed in another French department from 1995 to 1999 [7]. In Seine-Maritime the outbreak was due to *N. meningitidis* phenotype B:14:P1.7,16 belonging to the clonal complex ST-32/ET-5 and was associated with severe infections. This phenotype is not common in France. In 2003 an outbreak of six cases of this phenotype emerged in Metz, which led to a mass prophylaxis campaign for the 8000 people living in the affected area [6]. B outbreaks have been described in the 30 past years in Europe and America with common epidemiological characteristics: high attack rate among teenagers [8], presence of the strain for several years before the emergence of the epidemic [8] and high severity of the disease.

The high CFR and high incidence in teenagers gave the health authorities cause for concern, and justified targeted responses. Evidence suggests that awareness among healthcare professionals and the general population have contributed to minimise the waiting period before treatment and therefore to make the CFR decrease over the outbreak period [10,11].

Mass chemoprophylaxis for the population living in Dieppe and the surrounding areas was considered to be an ineffective response because the strain had already been shown to be present throughout the department, and any untreated members of the population could easily re-introduce the strain into the treated population, and contribute to the emergence of rifampicin resistance [12] and the elimination of non-pathogenic *Neisseria* which can help to boost immunity to meningococcal disease. The absence of a universal vaccine against serogroup B had prompted the development of protein-based, OMV vaccines that have proven to be efficacious against specific strains in Norway and Cuba [13,14]. OMV vaccine especially developed for New Zealand is currently being used in a mass vaccination campaign targeting young people below 20 years of age [15]. These vaccines may be effective against related strains. Vaccination with an OMV vaccine prepared on the basis of a closely related strain was discussed by the Ministry of Health in order to control the persistent outbreak in Seine-Maritime. In 2005, the number of IMD cases in the department continued to rise and the annual incidence was 3.4 per 100 000, with 42 cases. The B:14:P1.7,16 N. meningitis strain was isolated in Dieppe area as well as in the rest of the department and remained associated with high proportion of purpura fulminans and deaths.

On the advice of national vaccination advisory board, the Ministry of health decided in 2006 to offer all those aged between 1 and 19 years in Seine-Maritime vaccination with the Norwegian OMV vaccine developed against the B:15:P1.7,16 strain. The vaccination campaign dedicated to 1 to 19 years old population residing in Seine-Maritime started in June 2006 in Dieppe area and will be offered progressively to the rest of the population. Since June 2006, close contacts of identified B:14:P1.7,16 new cases occurring in France are also offered vaccination.

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