

- **Level 3** (intervention) activation relies principally on the InVS alert bulletin (**biometeorological threshold actually exceeded in at least one district, with forecasts for similar levels for the next two days**) or other available findings (excess human or animal mortality observed and associated with high heat, etc.). Local and national authorities then implement the plan's health and social measures: advisories for and specific care of persons.

- **Level 4** (requisition) is activated principally **when the biometeorological indicators forecast for the next 24 hours exceed the thresholds in several regions and/or for a long period, with collateral effects** (such as blackout, drought, or saturation of hospitals). Heat waves can induce crises with consequences that go beyond health and social effects. Exceptional measures must be applied to cope with such events.

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## • Local alerts

### Epidemic of community-acquired legionellosis around Lens

**On 28 November 2003, the Lens hospital informed the Pas-de-Calais district health bureau of two cases of community-acquired legionellosis. Both patients were residents of the municipality of Harnes and lived 400 m apart. Their clinical signs began on the 11<sup>th</sup> and 15<sup>th</sup> of November. The DDASS**

**Community-acquired (infection):** describes infections acquired in the community (that is, to which exposure occurred in the community) as opposed to nosocomial infections, acquired in a hospital.

**contacted the regional office of industry, research, and the environment (DRIRE) the same day and learned that it had been notified in mid-November of a substantial *Legionella pneumophila* contamination (>106 colony-forming units per liter or CFU/L) in Harnes. A petrochemical company there had detected contamination of its cooling towers during two regular in-house inspections, on 15 October and 20 November, and had implemented a plan to combat it as soon as it learned of the results. This news led DDASS to look for other cases at the Lens hospital and from local general practitioners. By 2 December, nine cases of**

**legionellosis had been identified, all residents of Harnes and the towns bordering it and with an onset in November 2003. DDASS and the regional epidemiology unit (CIRE) immediately began an epidemiologic investigation to confirm the epidemic nature of this phenomenon, to measure its importance, identify the origin and source of the contamination, and implement appropriate control measures.**

Data from this epidemiologic study revealed that this legionellosis epidemic was the largest community-acquired epidemic ever described in France—in terms of duration, geographic scope, and the number of cases involved. Retrospective

and prospective case-seeking in hospitals around Lens and other regional reference hospitals counted a total of 86 confirmed legionellosis cases due to *L. pneumophila* serotype 1, all with an onset between 5 November 2003 and 22

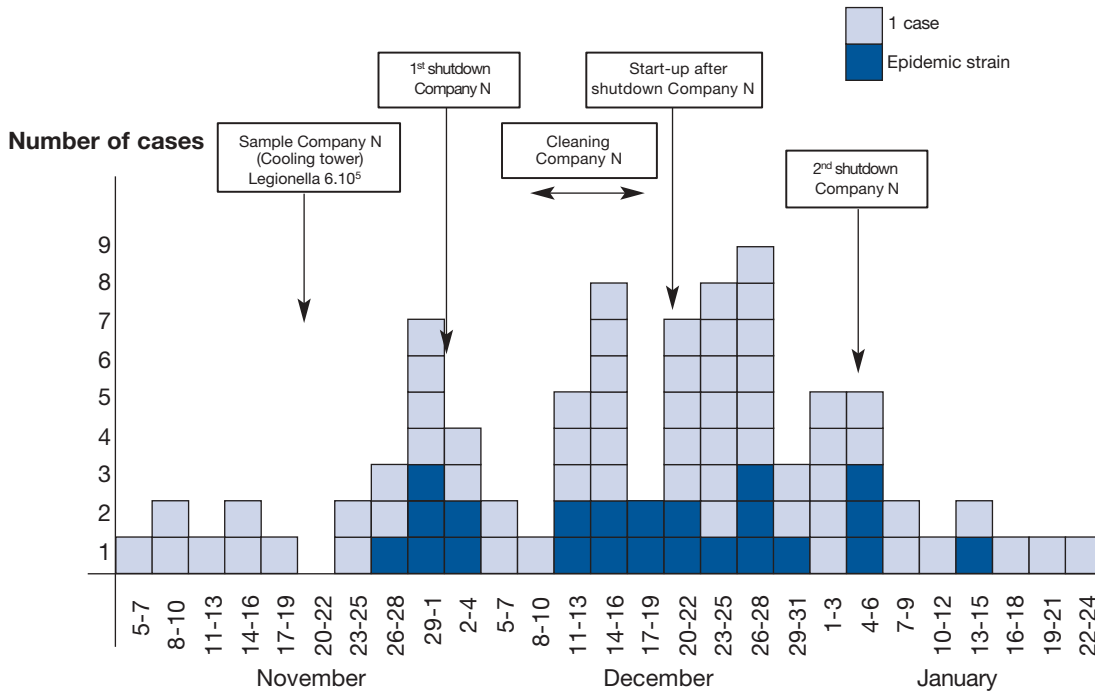
January 2004, in people living or having traveled in the Lens region; 17 people (20%) died.

The two-humped shape of the epidemic curve (Figure 8) suggests as a working hypothesis an intermittent and persistent source of contamination. No single location could be

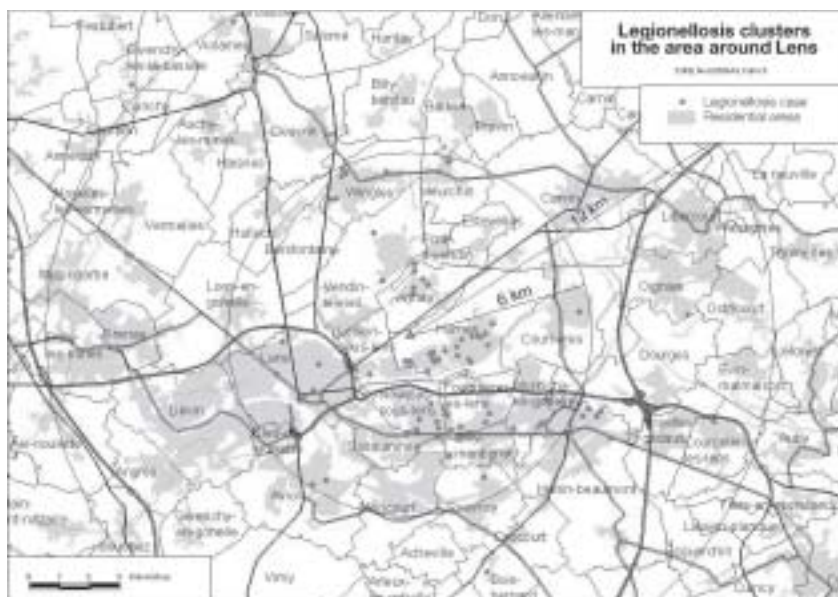
identified as having been visited by all the cases. With 23 cases and the highest attack rate of the 22 municipalities where cases lived, Harnes appeared to be the epicenter of the epidemic (Figure 9).

**Attack rate:** proportion of those becoming ill among the population exposed to an epidemic.

**Figure 8. Three-day distribution of legionellosis cases according to the date symptoms began (legionellosis epidemic, Pas-de-Calais, November 2003-January 2004)**



**Figure 9. Georeferenced distribution of cases according to home address (legionellosis epidemic, Pas-de-Calais, November 2003-January 2004)**



Source : © IGN - BD carto®, Paris (1999)

### – Bacteriological and environmental testing

*L. pneumophila* serogroup 1 was isolated in 23 (47%) of the 49 patients from whom bronchial samples were obtained. All the clinical strains presented the same genomic profile after

**Serogroup or serotype or serovar:** category in which bacteria or viruses are classified according to their reaction in the presence of serum containing specific antibodies. This serologic variety is a subdivision of the species.

pulsed-field electrophoresis, and this strain was isolated in cases throughout the epidemic. This profile had not previously been identified in the strain collection of the legionella national

reference center (CNR).

At the same time, the DRIRE and the DDASS conducted environmental studies in 53 municipalities around Lens and at 33 companies that operated cooling towers; they identified **two environmental sources emitting the epidemic strain in Harnes besides company N:** an agri-food company and a car wash. Legionella concentrations at company N (cooling towers

and waste lagoon) were clearly higher than those at the other sites (Table 3), and their involvement in the onset of the epidemic appears improbable (because the epidemic strain was not found in the cooling towers of the agri-food company at the initial stages of the investigation and because of the architectural configuration of the car wash). Their proximity to company N (less than 1 km as the crow flies) may explain their secondary colonization by the epidemic strain it emitted.

Company N shut down completely on 3 December and disinfected again. Nonetheless, an upsurge in the epidemic began in mid-December and studies showed persistent contamination of company N's cooling systems. This persistence, which probably contributed to the continuation of the epidemic, may have resulted from high-pressure cleaning operations, the difficulties of disinfecting the entire system (oxbows, or abandoned channels), or recontamination of the cooling towers from the system aerating the waste lagoon surface, which was seeded with biological sludge contaminated by the epidemic strain.

**Table 3. Sites from which the epidemic strain was isolated (legionellosis epidemic, Pas-de-Calais, November 2003-January 2004)**

Site		Sampling date	Sampling location	Result date	CFU <i>Legionella</i> / L	CFU <i>L. pneumophila</i> serogroup 1/L
Company N	Cooling towers	28/11/03	Hot pond	23/12/03	2400	2100
		30/12/03	Cooling pond	14/01/04	1000	1000
	Effluents	01/12/03	Entry to containment pond	23/12/03	910 000	340 000
		08/01/04	Waste lagoon	30/01/04	210 000 000	5 000 000
		08/01/04	Waste lagoon seeds	30/01/04	11 000 000 000	1 000 000 000
Car wash		19/12/03	Manifold nozzle	05/01/04		1600
Agri-food company	Cooling towers	29/12/03	Hot water tank	19/01/04	100	100

CFU: colony-forming unit

**The combination of descriptive epidemiology, environmental studies, and molecular biology (determination of serogroup and genomic profile of the epidemic strain) made it possible to reconstruct the chain of transmission. Suspicion thus fell on airborne**

**contamination from company N's legionella-contaminated cooling system. The progressive extinction of the epidemic after the complete shutdown of all identified at-risk activities at company N reinforced these hypotheses.**

This epidemic was the first in France with an industrial facility involved in the onset of community-acquired legionellosis. The extensive geographic dispersion of the cases observed in this epidemic had never before been reported. The regional weather conditions (wind and humidity) and topology (semiurban plain) probably contributed to the extensive diffusion of legionella-contaminated aerosols. The national institute of the environment and industrial risks (INERIS) used statistical modeling techniques to evaluate the aerosol emissions from Company N; their findings suggest that although the risk of population exposure to legionella aerosols clearly diminishes beyond 2 km from the source, it may exist in an area on the order of 10 km around the factory. Ongoing analytic studies and consideration of the meteorologic factors may provide additional support for these hypotheses.

The onset of this epidemic in winter was also unusual. All other legionellosis epidemics so far reported in France and caused by cooling towers began during the

#### Recommendations:

The lessons from the investigation of this epidemic are that prevention activities must be reinforced and that improved risk assessment and risk management are essential for legionellosis associated with industrial cooling towers.

Collective prophylaxis requires:

- an exhaustive census of the systems at risk
- improvement of good maintenance practices and their diffusion to owners and companies providing maintenance of cooling towers
- reinforced monitoring of systems at risk
- strict application of official recommendations in cases of contamination
- notification of health authorities in cases of substantial contamination of facilities at risk
- reinforced vigilance by health authorities of possible sources of community-acquired contamination.

summer (June–September). The strain responsible for the epidemic in the Lens region thus seems particularly resistant to climate conditions unpropitious to legionella development.

## Human and equine infection with West Nile virus in the Var

On 6 October 2003, the arbovirus national reference center reported West Nile meningoencephalitis in a resident of the Var district who was hospitalized in Nice. On 9 October, a case of equine West Nile encephalitis was reported by AFSSA, the French food safety agency, in a horse living in another area of the Var. On 17 October, the arbovirus CNR confirmed that the patient's wife, who had not left the district, was also infected by West Nile virus. The surveillance for West Nile virus already covering Camargue and Corsica was then extended to the Var and all other French districts along the Mediterranean (Pyrénées-Orientales, Aude, Alpes-de-Haute-Provence, Alpes-Maritimes), with (human and equine) epidemiologic and entomological studies conducted to explore virus circulation in these districts.

– A retrospective and prospective study was conducted in healthcare facilities to identify cases of meningitis, meningoencephalitis, and polyradiculoneuropathy with no known cause. It found seven confirmed cases of West Nile virus infection. The patients all lived in the eastern Var and felt their first symptoms during the last half of August (Figure 10); three patients had neurological

forms of the disease, while the other four had influenza-like illnesses. The infection resolved favorably in all cases.

No human case with an onset of symptoms after 28 August was identified in the Var or any district along the Mediterranean in 2003.

– **Active surveillance of equine encephalitis**

ascertained four confirmed cases in western Var, all with symptoms that began in September (Figure 10). A probable equine case with no symptoms was identified in the herd of one of the other equine cases.

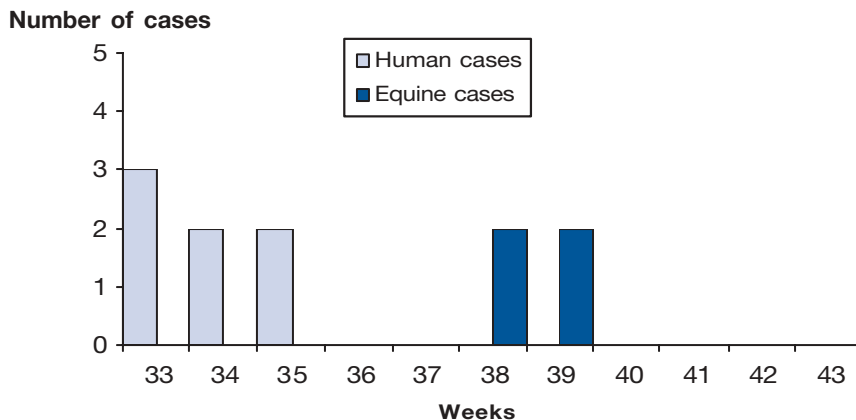
– **The Mediterranean interdistrict antimosquito**

group (EID) conducted entomological field surveys on the premises where the human and equine cases lived. Because not many mosquitoes remain in early October, few were captured. The "emerging virus" unit at the University of Marseille tested them for West Nile virus, with negative results.

These studies showed that viral circulation was limited to the Var and to the months of August and September 2003. The Var district veterinary bureau took blood samples from approximately 1000 horses in the district, to study the circulation of West Nile virus in this equine population.

The French blood agency also surveyed blood donors in the Var and other Mediterranean districts to estimate the risks of virus transmission by transfusion of blood from asymptomatic contaminated donors.

**Figure 10. Date of onset of signs in human and equine cases, confirmed and probable (West Nile virus infections, Var, August-September 2003)**



### Infection and colonization by multidrug-resistant *A. baumannii* in healthcare facilities in several districts

During the second half of 2003, several healthcare facilities, located mainly in the districts of Nord and Pas-de-Calais, reported cases of *Acinetobacter baumannii* infection or colonization that were resistant to several antibiotics; all the strains isolated had the same resistance profile. The national alert that followed these reports led to the identification of similar cases in other facilities in France. It also resulted in reinforcing measures for the prevention and control of multidrug-resistant bacteria diffusion, especially during the transfer of patients from one healthcare facility to another.

– **Alert**

From 30 July through 19 September 2003, four healthcare facilities in the Nord district transmitted five reports of nosocomial infections by *A. baumannii* to the nosocomial infection control coordinating center (CClin), the DDASS, and InVS; these concerned 23

patients, 8 of whom had died by the time of the report. The *A. baumannii* strain responsible, with its worrisome resistance to multiple antibiotics, had been isolated and identified for the first time in the Nord in July 2001. However, these resistance characteristics facilitate its identification (sidebar). It produces an

enzyme (extended-spectrum beta lactamase, or ESBL, VEB-1 type) that makes it resistant to all beta-lactams. The strain is now sensitive to only two antibiotics: imipenem and colistin.

While *A. baumannii* is not pathogenic in healthy individuals, it is frequently resistant to numerous antibiotics and responsible for nosocomial infections in units that treat vulnerable patients (intensive care, for example). In weakened patients, it causes various infections, sometimes severe (pulmonary infections, septicemia, and wound or burn infections). It does not always cause infection and may simply be present on the patient's skin or mucous membranes (colonization or carriage rather than infection). It can persist for a long time in the environment and its transmission is hand-to-hand.

In an uncontrolled epidemic context, the appearance of a strain that might become resistant to imipenem was a distressing possibility that justified a national alert to identify all of the facilities affected and to reinforce the measures for prevention and control of the diffusion of multidrug-resistant bacteria.

#### – Methods

The alert network for the investigation and surveillance of nosocomial infections (RAISIN) notified all healthcare facilities of the emergence of this strain of *A. baumannii* in France and of its characteristics; all cases of infection or colonization with this strain were to be reported.

#### • Case definition

A probable case was defined as any patient infected or colonized since April 2003 by a strain of *A. baumannii* with an antibiotic

resistance profile similar to that of the strain isolated in 2001; its characteristics were widely distributed to microbiology laboratories to help them identify it; its resistance phenotype is reviewed below (sidebar). The definite cases were those for which the expert laboratory confirmed VEB-1-type ESBL production. The distinction between colonization and infection relied on the clinical information available and on the definitions contained in the "100 recommendations for surveillance and prevention of nosocomial infections" manual.

#### • Investigation

The investigation received support by RAISIN (CCIin and InVS), help from the DDASS, and expertise from the bacteriology-virology-hygiene department at the Bicêtre UHC (Le Kremlin-Bicêtre, 94). Each report was investigated by the facility's operating hygiene team, assisted if necessary by the CCIin or the DDASS. The aim of these studies was to confirm the cases and implement the appropriate control measures. The data collected were transmitted to InVS to enable monitoring of the diffusion of this strain nationwide.

#### – National assessment as of 2 June 2004

As of 2 June 2004, 54 healthcare facilities in 15 districts (covering 8 regions) had reported 290 probable cases of infection or colonization by *A. baumannii* presenting the same antibiotic resistance profile and diagnosed between 22 April 2003, and 14 May 2004 (Figure 11); 255 (88%) cases were identified by the nosocomial infection reporting system and 35 (12%) additional cases by the expert laboratory.

### The phenotype of antibiotic resistance of the extended-spectrum $\beta$ -Lactamase VEB-1-producing isolates of *A. baumannii* (reference: *Journal of Clinical Microbiology* 2003; (41): 3542-7)

a) Disk diffusion susceptibility testing on agar plates showed the following phenotype:

- S to imipenem (IPM) and colistin (CS);
- I or R to the combinations of ticarcillin/clavulanic acid (TCC) and piperacillin/tazobactam (TZP);
- R to ticarcillin (TIC) and to third-generation cephalosporins: ceftazidime (CAZ), cefotaxime (CTX), and cefepime (FEP).

Comment: no inhibition diameter for TIC, CAZ, CTX, or FEP;

- R to ciprofloxacin (CIP), cotrimoxazole (SXT), tetracycline (TE), gentamicin (GM), tobramycin (TM), netilmicin (NET), and amikacin (AN).

Comment: sensitivity to aminoglycosides can vary according to the strain.

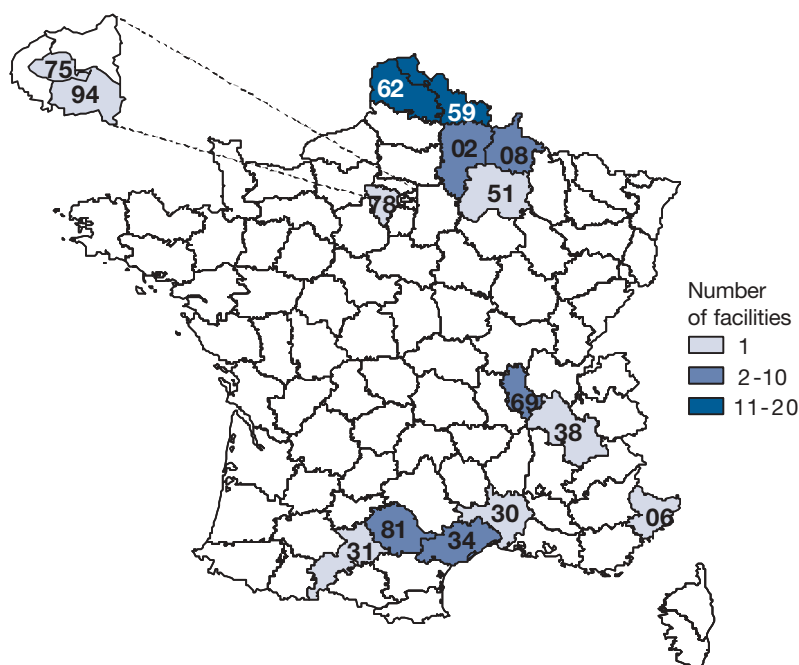
b) Demonstration of synergy between the FEP and/or CAZ and TCC disks, suggestive of ESBL.

Of 290 cases, 217 (75%) were clinically documented: 73 (33%) were infections and 144 (67%) colonizations. Of 288 strains of *A. baumannii* transmitted to the expert laboratory in addition to the reported cases, 275 (95%) were confirmed to be ESBL VEB-1-producing isolates. All the strains studied were still sensitive to imipenem.

Among the 290 cases reported, 34 patients (11%) had died by the date of the report. These deaths were not all associated with the infection; in December 2003, Paris-North Cclin data showed

that 57% of the deaths could be attributed to the infection, and then it was not always the only short-term cause of death.

**Figure 11. Number of facilities reporting at least one case of infection or colonization with ESBL-producing *A. baumannii* in France, April 2003-May 2004 (N=54)**



**Table 4: Infections or colonizations with ESBL VEB-1-producing *A. baumannii*. Number of facilities, number of cases reported and date of last case, by district, France, July 2003-May 2004**

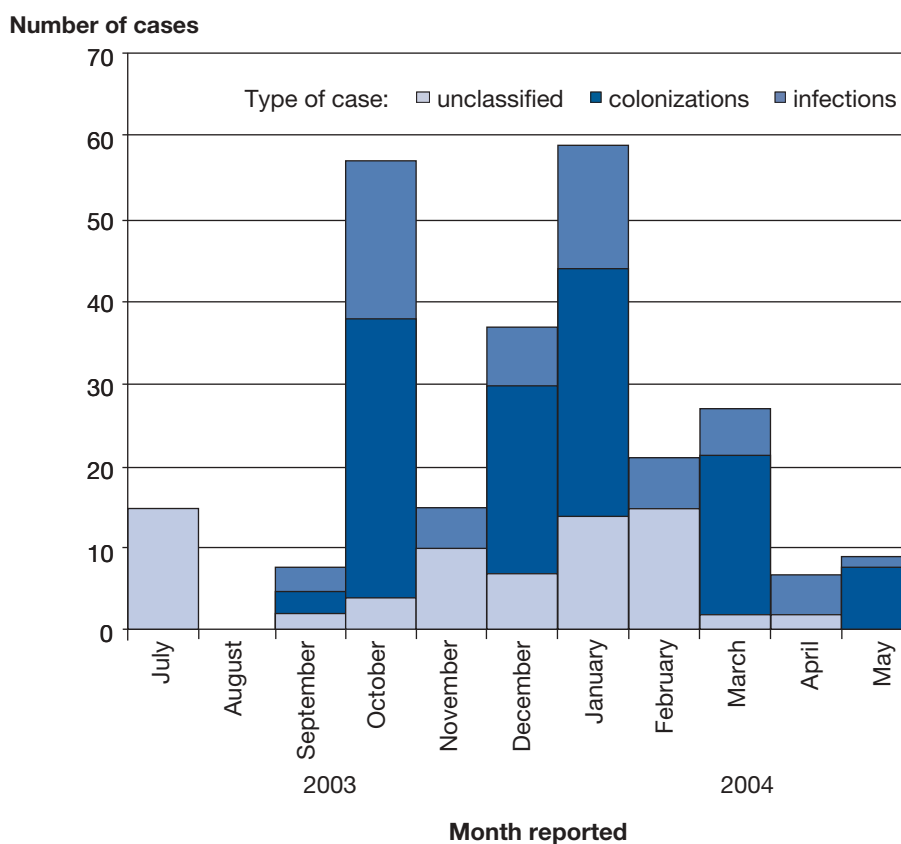
District	Facilities (N)	Cases reported (N)				Death (N)	Date of last case
		Total	By status				
			Infected	Colonized	Unknown		
59 - Nord	20	124	19	60	45	24	13/05/04
62 - Pas-de-Calais	14	111	32	55	24	7	14/05/04
02 - Aisne	2	2	0	0	2	0	05/11/03
75 - Paris	1	1	1	0	0	0	31/01/04
78 - Yvelines	1	1	0	1	0	0	08/03/04
94 - Val-de-Marne	1	1	1	0	0	0	03/05/04
08 - Ardennes	2	14	6	8	0	0	02/02/04
51 - Champagne	1	11	2	9	0	1	15/03/04
31 - Haute-Garonne	1	5	1	2	2	1	15/04/04
81 - Tarn	2	2	1	1	0	0	05/01/04
34 - Hérault	2	7	5	2	0	1	09/04/04
30 - Gard	1	1	1	0	0	0	10/04/04
69 - Rhône	4	8	4	4	0	0	07/02/04
38 - Isère	1	1	0	1	0	0	02/12/03
06 - Alpes-Maritimes	1	1	0	1	0	0	03/01/04
<b>Total</b>	<b>54</b>	<b>290</b>	<b>73</b>	<b>144</b>	<b>73</b>	<b>34</b>	<b>14/05/04</b>

Note: districts reporting new cases diagnosed since 1 April 2004 appear in blue rows.

Table 4 summarizes the distribution of the cases reported by district. Most of the cumulative cases (235/290, or 81%) came from the Nord-Pas-de-Calais region. The national alert nonetheless enabled early identification of new outbreaks in Midi-Pyrénées, Languedoc-Roussillon, Rhône-Alpes, PACA, and Ile-de-France: the isolation of similar strains in the regions that had not previously reported any cases retrospectively justified the national alert. While the transfer of patients between healthcare facilities explained the substantial diffusion of

this strain in Nord-Pas-de-Calais, no documented transfers explain its diffusion to the other regions. By June of 2004, the diffusion of this multidrug-resistant strain had clearly slowed; since January, the number of new cases reported fell regularly (Figure 12). Several residual outbreaks persisted in the districts of Nord, Pas-de-Calais, Haute-Garonne, Hérault, and Gard and justify the maintenance of a minimal level of vigilance as part of the regular reporting channel. The last reported case came from Pas-de-Calais.

**Figure 12. Number of infections and colonizations by ESBL VEB-1-producing *A. baumannii*-1 in France, by month reported, July 2003-May 2004 (N=255)**



#### – Control and prevention measures

Controlling an epidemic of *A. baumannii* requires major efforts: strict compliance with standard hygiene procedures (hand washing), careful cleaning of surfaces, implementation of protocols for isolation, systematic screening of carrier patients, reporting these patients on transfer, and, in extreme cases, temporary

shutdown of the department.

In October the Paris-North CCLin distributed recommendations for the surveillance and control of these infections to all healthcare facilities in the Nord-Pas-de-Calais region; also in October, InVS transmitted through RAISIN recommendations to the other CCLins for surveillance, alert, and control.

### Recommendations of the Paris-North CClin to healthcare facilities in the Nord-Pas-de-Calais region, September 2003

1. Report (decree of 26/07/01) all cases of infection and/or colonization by BLSE-producing *A. baumannii* to the CClin and the DDASS and attach the antibiogram results to the report form.
2. Conserve suspicious strains and contact the expert laboratory to decide whether they should be sent for microbiological expertise.
3. Inform the facility's medical and paramedical teams that this epidemic strain is circulating in the region.
4. Plan systematic screening (axillary, pharyngeal, and rectal) in high-risk departments (such as intensive care).
5. Limit internal movement of patients as well as their transfer to other units, unless necessary.
6. Report on the transfer form and in the patient's medical file at transfer the status as a carrier of multidrug-resistant *A. baumannii* (as recommended for other multidrug-resistant bacteria, including MRSA and ESBL-producing enterobacteria).
7. Reinforce measures of isolation and compliance with standard precautions for infected or colonized patients in any department.
8. Reinforce procedures for biocleaning in the departments in which cases were identified.
9. Monitor appropriate usage of antibiotics in the departments at risk (intensive care and pulmonary medicine).

### RAISIN recommendations to the CClin, October 2003

The Institute of Public Health Surveillance recommends to the CClin and to the coordinators of their multidrug-resistant bacteria surveillance networks that they:

1. inform their standard distribution lists (Clin president, operational hygiene team, microbiology laboratories) of the epidemic of *A. baumannii* identified in northern France
2. request healthcare facilities in their region to report (decree of 26/07/01) all cases of infection and/or colonization by ESBL-producing *A. baumannii* to the CClin and the DDASS, attaching an antibiogram to the report form
3. inform InVS without delay of any new case
4. request healthcare facilities to conserve suspicious strains and contact their usual reference laboratory for advice;
5. distribute to the healthcare facilities in their region recommendations for prevention and control of *A. baumannii* infections appropriate for the regional or national epidemic situation.

#### – Conclusion

The recent emergence and diffusion of this strain of multidrug-resistant *A. baumannii* is worrisome. It underlines the usefulness of the alert (reporting) networks established several

years ago for detection of emerging nosocomial infections and of compliance by healthcare facilities with existing recommendations for control of multidrug-resistant bacteria.

### Clusters of kidney cancer cases among employees of the Adisseo factory at Commentry (Allier)

In early January 2003, the Ministries of Health and of Labor jointly referred to InVS for investigation the reports of kidney cancer cases among employees of a chemical plant that manufactures vitamins A and E as well as methionine, an additive for animal food supplements. This plant, which dates back to the beginning of the last century, is located at Commentry, in the Allier district. It did and does use many products and generates intermediate chemical substances at various stages of synthesis; these include chloracetal C5, which is used to fabricate vitamin A and is thought by some experts to be the causal agent for the cancers observed.

**InVS first verified the reality and size of the kidney cancer cluster observed at Adisseo. InVS's department of occupational health (DST) then launched epidemiologic investigations in several stages to verify the plausibility of a workplace origin for these cases. The Pasteur Institute of Lille—at the company's initiative, with advice from the national research and safety institute (INRS)—conducted toxicological studies, especially of chloroacetal C5.**

Kidney cancers accounted for 3% of new cancer cases diagnosed in France in 2000. Estimates indicate new cases are diagnosed annually in 5306 men and 2987 women, while 2329 men and 1278 women die of this cancer in a year. The incidence rates of kidney cancers are rising substantially in most developed countries, although mortality remains stable. The fortuitous discovery of kidney tumors during imaging examinations for reasons other than suspected kidney cancer probably explains this increased incidence, but the role of other factors in this increase has not been ruled out.

Currently, smoking, obesity, and hypertension are the only suspected risk factors for kidney cancer. Epidemiologic studies of occupational risk factors observe an increased, albeit inconsistently, risk of kidney cancer with diverse occupations and hazards, including asbestos, polycyclic aromatic hydrocarbons, trichloroethylene, gasoline, other petroleum derivatives, lead, and cadmium. One study showed a statistically significant association with an exposure-effect relation between kidney cancer and exposure to vinyl chloride monomer.

#### – Initial verification

- **Verifying the reality of the cases reported**

The company's occupational physician provided documentation that the 10 cases of kidney cancers between 1994 and 2002 were indeed real. All were confirmed by cytopathologic examinations that showed adenocarcinoma in all the cases. The tumors were all identified at an infraclinical stage; the patients all underwent surgery (total or partial nephrectomy), and all remain alive to date.

It should be noted that this screening took place as part of medical monitoring by the occupational physician: systematic abdominal ultrasound, initially intended as medical surveillance for workers exposed to vinyl

chloride monomer, a known hepatic carcinogen (group 1 of the International Agency for Research on Cancer or IARC), and then extended to other populations after the first kidney cancers were identified by the occupational physician.

**Cytopathology:** branch of medicine that examines organs or tissues microscopically to study the lesions caused by diseases. Today it uses many techniques (electronic microscopy, tissue culture, histochemistry, histoenzymology, immunology, radioisotope labeling).

- **Verifying that there were more kidney cancers than expected**

The DST calculated the standardized incidence ratio (SIR) from information provided by the company's occupational medicine department about the incident cases observed (date of birth, date of diagnosis, sex) and by the company about its employee population (number of employees by age group and by sex, for every year from 1994 through 2002). These calculations concerned only men, since no cancer had been reported among the women at the company at that point.

When the national incidence rates for kidney cancer in men, estimated from French cancer registry data, are applied to the population of men at the company, less than one case of kidney cancer (0.76) is expected over the entire period. The SIR was 13.1 (95% CI: 6.28–24.10). This very high SIR is statistically significant and confirms the excess of cases among the men working at this factory.

#### – Cohort study

The objective of this study is to analyze the mortality from cancer (and specifically from kidney cancer) in this company compared with the French

**Standardized incidence ratio (SIR):** comparative incidence ratio: relation between the number of cases observed and the number of cases expected. This is the indirect standardization method in which we calculate the number of events expected in the study population by applying to it (for each age group) the specific rates of a reference population.

population and with other company employees, according to specific occupational characteristics (for example, social and occupational category, worksite, occupation, specific hazards), to identify possible company activities or sectors more particularly at risk.

This historic cohort was defined as all employees who had worked at this site for at least six months in 1960 or after. Examination of the different data sources available about the plant site led to the decision to reconstruct the cohort to use the information from the annual social data declarations, available as of 1952. Pay slips from the various employment periods since 1960 will make it possible to collect additional information about the specific departments to which employees with non-administrative jobs (production, maintenance, and laboratory) were assigned. This will enable us to establish a more detailed occupational history and to analyze the causes of death as a function of specific job sites and possible hazards particular to them.

The data collected from these two sources should make it possible to reconstruct **the cohort, which should include approximately 2800 subjects.**

**– Nested case-control study in the cohort study**

The objective of this nested case-control study is to identify possible occupational factors and exposures associated with the excess of kidney cancers observed among these employees and to suggest etiological hypotheses. This type of study requires interviewing relatively few subjects, limits the selection bias of the control population, and obtains detailed information about occupational and non-occupational exposures.

The study will consider cases of kidney cancer already identified by the occupational medicine department and those that may be found by further specific research. Because systematic screening for kidney cancers by abdominal ultrasound is part of the standard occupational

medicine examinations of some groups of employees exposed to chemical hazards, supplementary cases must also be sought among employees not subject to this screening or before it was implemented (1986 for some occupational groups).

This research involves three regional sources:

- hospitals: research from the PMSI (medical informatics system) database for the 1997-2001 period, from medical files for previous years, in four hospitals in the Allier and Puy-de-Dôme districts in which subjects living in the same area as the current employees have frequently been treated for kidney cancer;
- pathology laboratories: through the president of the national federation of pathology statistics and data centers (CRISAP), the DST obtained a list of subjects diagnosed with kidney cancer in the five regional pathology laboratories that specialize in this diagnosis;
- and the regional health insurance fund: after approval by the national consulting physician at the CnamTS, DST obtained the list of subjects receiving complete reimbursement for kidney cancer as a "long-term disease" (ALD30) in Allier and Puy-de-Dôme.

The population of controls will be composed of employees of or retirees from the factory who do not have kidney cancer, chosen from within the cohort and matched for sex, age, and vital status.

The information for cases and controls will be collected with a standardized questionnaire including one occupational and one general section.

**Analysis of the causes of death of the reconstructed cohort will begin in late 2004. Analysis of the nested case-control study is planned for 2005. The feasibility of conducting a study of the impact of active screening for kidney cancer by systematic abdominal ultrasound will be studied in 2004.**