

A Community-Wide Outbreak of Legionnaires Disease Linked to Industrial Cooling Towers—How Far Can Contaminated Aerosols Spread?

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A community-wide outbreak of legionnaires disease occurred in Pas-de-Calais, France, in November 2003–January 2004. Eighteen (21%) of 86 laboratory-confirmed cases were fatal. A case-control study identified smoking, silicosis, and spending >100 min outdoors daily as risk factors for acquiring the disease. *Legionella pneumophila* strain Lens was isolated from cooling towers, wastewater, and air samples from plant A. This unique strain matched all 23 clinical isolates, as assessed by pulsed-field gel electrophoresis subtyping. Modeling of atmospheric dispersion of aerosols emitted from plant A cooling towers showed good coverage of the communes where patients lived and showed that the dispersion extended over a distance of at least 6 km from plant A. No other aerosol-producing installation was identified as a plausible source, and no common source of indoor exposure was found. These findings implicate plant A as the most likely outbreak source and suggest that the distance of airborne transmission of *L. pneumophila* may be greater than previously reported.

Legionnaires disease (LD) is an atypical pneumonia caused by bacteria of the genus *Legionella* [1, 2]. Investigations of outbreaks have demonstrated that in-

halation of aerosolized water containing *Legionella* bacteria is the primary mode of acquiring LD. Widely reported sources linked to outbreaks include cooling towers (CTs) [3–11] and other aerosol-producing devices [12–18]. CTs can give rise to large outbreaks accounting for hundreds of LD cases [10, 11], because of their capacity to disperse contaminated aerosols over long distances. The complex interaction between bacteria, host (both human and protozoan), and environmental conditions (including CT aquatic biosystems) that leads to an outbreak of LD remains poorly understood [19].

On 28 November 2003, 2 LD cases were reported to public-health authorities in Pas-de-Calais District, northern France. The patients resided in Harnes, a rural commune of ~14,000 inhabitants. On the same day, the local environmental authority revealed that routine self-sampling had recently detected high levels of *Legionella* bacteria in the CTs of a petrochemical plant (plant A) in Harnes. Identification of 2 LD cases and contaminated CTs in the same commune triggered an alert and further investigation. The objectives of this investigation were to determine the magnitude of the outbreak,

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to identify source(s) of transmission and risk factors for acquiring LD, to implement control measures to prevent further transmission, and to evaluate the effectiveness of these control measures.

METHODS

Case definition and case investigation. A confirmed case of LD was defined as a person who (1) had radiologically confirmed pneumonia and laboratory evidence of infection with *Legionella pneumophila* serogroup 1 (Lp-1) (i.e., isolation of Lp-1 from respiratory secretions, detection of Lp-1 antigens in urine, or a minimum of a 4-fold increase [to ≥ 128] in antibody titers to Lp-1), (2) became ill between 1 November 2003 and 31 January 2004, and (3) lived in or visited Harnes or its neighboring communes during the 10 days before the illness. Persons who had been hospitalized or traveling continuously outside of the community during the 10 days before the illness were excluded.

In France, physicians and microbiologists are required to notify confirmed and probable cases of LD [20]. In addition, an active search for cases was initiated among physicians, laboratories, and hospitals in Harnes and its 3 adjacent communes on 2 December 2003 and was extended to communes located within 12-km radius of Harnes (defined as the epidemic zone) on 30 December 2003. All cases were interviewed using a standardized questionnaire to collect information on current illness, place of residence, mobility, and personal characteristics and environmental factors known to be associated with LD.

Matched case-control study. On 15 January 2004, a matched case-control study was initiated to identify risk factors related to personal characteristics, activities, and potential exposure to contaminated aerosols. Confirmed cases living in communes where at least 2 cases had been identified were included in the study. Controls were randomly selected from the municipal electoral list. Three controls were matched to each case, according to commune of residence, age (10-year groups), and sex. Cases and controls were interviewed face-to-face within 3–4 weeks after the illness of the case. A standardized questionnaire with ~150 variables solicited 3 types of information: (1) medical history and personal characteristics, (2) housing and living conditions, and (3) daily outdoor activities and exposures in the 10 days before the illness of the case. To estimate the cumulative exposure to outdoor air, subjects were asked about each outing (defined as an exit from the home), means of transportation used (car, bike, foot, etc.), and time spent in each place during the period.

On the basis of preliminary univariate analysis ($P < .25$) and biological or epidemiological plausibility, variables were selected for a conditional logistic-regression model (using backward

elimination), to estimate risk factors for illness. Statistical analysis was performed using STATA (version 8.2; StataCorp).

Environmental investigation. Household water from cases' homes was systematically sampled. Locations of CTs and other industrial cooling systems in the epidemic zone were obtained from a census performed by the local environmental authority. Site inspections, record reviews, and water sampling were performed on these installations, as well as on other potential sources of contamination. These included municipal portable water systems, wastewater treatment plants, wells, canals, decorative fountains, air-conditioning systems in public buildings, car-wash stations, and other installations/devices capable of aerosol dissemination. Preventive decontamination was subsequently performed on installations that had levels of *Legionella* bacteria ≥ 1000 cfu/L. Weekly control sample collection was performed on all CTs until 15 February. Air samples were collected using a prototype of microbial air sampler (Cyclone; CSTB).

In plant A, operation and maintenance procedures of CTs, cooling units, wastewater treatment facilities, and other aerosol-producing water sources were investigated. To identify potential reservoirs of *Legionella* bacteria, cooling water, surface water, soil, and air from multiple sites on the premises of the plant were sampled. In addition, an environmental risk assessment of operation and control measures implemented at the plant was conducted.

Microbiological investigation. Diagnostic tests at the local hospitals included a urinary antigen test for Lp-1 (Now *Legionella*; Binax) [21], culture, and an indirect immunofluorescence test for serum antibody against *L. pneumophila* [22]. *Legionella* bacteria were isolated from environmental samples in accordance with the standard AFNOR NFT90-431 procedure [23] and were identified to the species and serogroup level by direct immunofluorescence and random amplified polymorphic DNA polymerase chain reaction [24]. All clinical and environmental isolates of Lp-1 and a selection of environmental isolates of *L. pneumophila* serogroups 2–15 were analyzed using the pulsed-field gel electrophoresis–*Sfi*I method [25].

Modeling of aerosol dispersion. A Gaussian dispersion model, ADMS 3 [26], was used to simulate the dispersion of presumably infectious aerosols from the CTs of plant A. The flat topography of the area allowed the model to simulate the aerosol dispersion on a horizontal scale over the epidemic zone on the basis of the following parameters: the emission parameters of plant A (including CT configuration, capacity, mode of function, and cleaning operations) and hourly meteorological data during the corresponding period (temperature, humidity, nebulosity, and wind speed and direction). Geographical information systems analysis was performed in ArcMap (version 8.3; ESRI).

Table 1. Demographic characteristics and underlying medical conditions of 86 legionnaires disease cases, Pas-de-Calais, France, November 2003–January 2004.

Characteristic	Cases, no. (%)
Male	52 (60)
Age >60 years	72 (84)
Health status	
Underlying medical condition or treatment ^a	64 (74)
Heavy alcohol intake (80 cc/day)	44 (51)
Current smoking	29 (34)

NOTE. Legionnaires disease was confirmed by urine antigen testing, culture, or serologic testing.

^a Included ≥ 1 of the following medical conditions or treatments: diabetes, chronic obstructive pulmonary disease, cardiovascular disease, renal disease, dialysis, transplantation, malignancy, chemotherapy, oxygen therapy, and use of corticosteroids.

RESULTS

Descriptive epidemiology. Of 104 cases notified between 1 November 2003 and 31 January 2004, 86 were confirmed as having LD; 84 (98%) had positive urine antigen test results, 23 of whom also had positive cultures, and 2 had experienced seroconversion. The median age of the cases was 76 years (range, 32–92 years), and the male:female ratio was 1.5 (table 1). Eighty-four cases (98%) were hospitalized, and 18 (21%) died. The demographic characteristics, underlying medical conditions, and median delay (4 days) between illness onset and diagnosis did not differ between those with fatal and nonfatal illness.

The shape of the epidemic curve suggested that there were 2 major infection waves: the first wave (26 cases) occurred from

5 November to 9 December, and the second (60 cases) occurred from 11 December to 22 January (figure 1). The attack rate for residents of the 22 affected communes was 3.9/10,000 population, which was >20 times higher than the national incidence rate in 2003 (0.18/10,000 population). The highest commune-specific attack rate (16.7/10,000 population) was observed in Harnes, which appeared to be the outbreak epicenter (figure 2). Forty cases (47%) lived in Harnes or in 3 adjacent communes, 70 (81%) lived in 15 communes located within a 6-km radius of Harnes, and 83 (97%) lived in 22 communes located within a 12-km radius of Harnes. Thirty cases (35%) did not leave their commune of residence, and 12 (14%) did not leave their home during the 10 days before illness (figure 2).

Sputum specimens from 49 (57%) cases were tested, and Lp-1 was isolated in 23 (27%). All clinical isolates shared an identical and unique pulsed-field gel electrophoresis pattern (figure 3) that did not match any (of >2000) genotypes in the National Reference Center databank. This epidemic strain, whose entire genome has been subsequently sequenced, was termed “Lp-1 Lens” [27]. The 23 culture-positive cases were found throughout the outbreak period (figure 1), and all but 1 lived in or visited an area within a 6-km radius of Harnes (figure 2).

Case-control study. Fifty-nine confirmed cases and 177 controls from 12 communes were included in the case-control study. The response rates among cases and controls were 91% (59/65) and 72% (177/246), respectively. The distributions of cases and controls according to sex, age, and commune of residence were identical. The following variables were included in a multivariable model: all known risk factors related to underlying

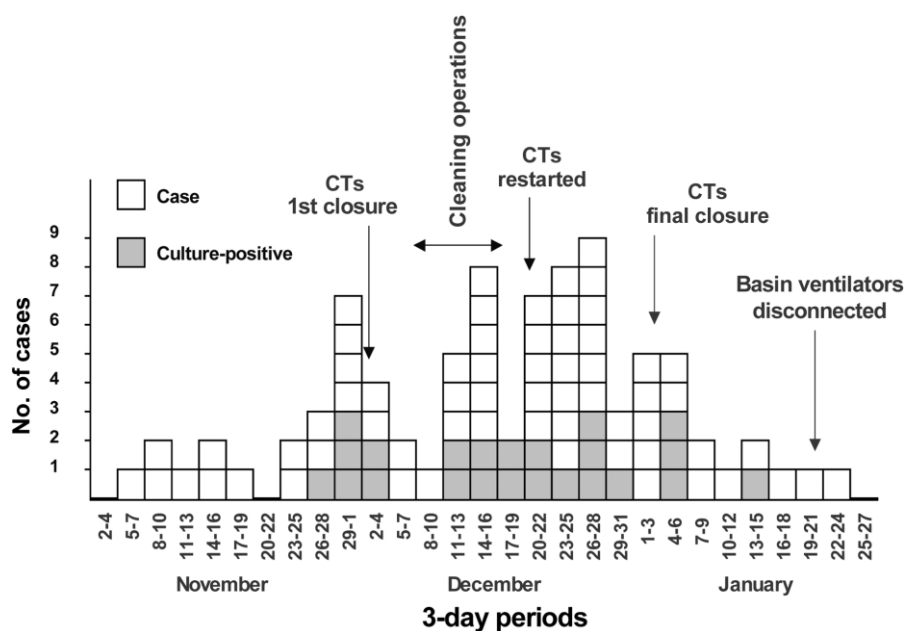
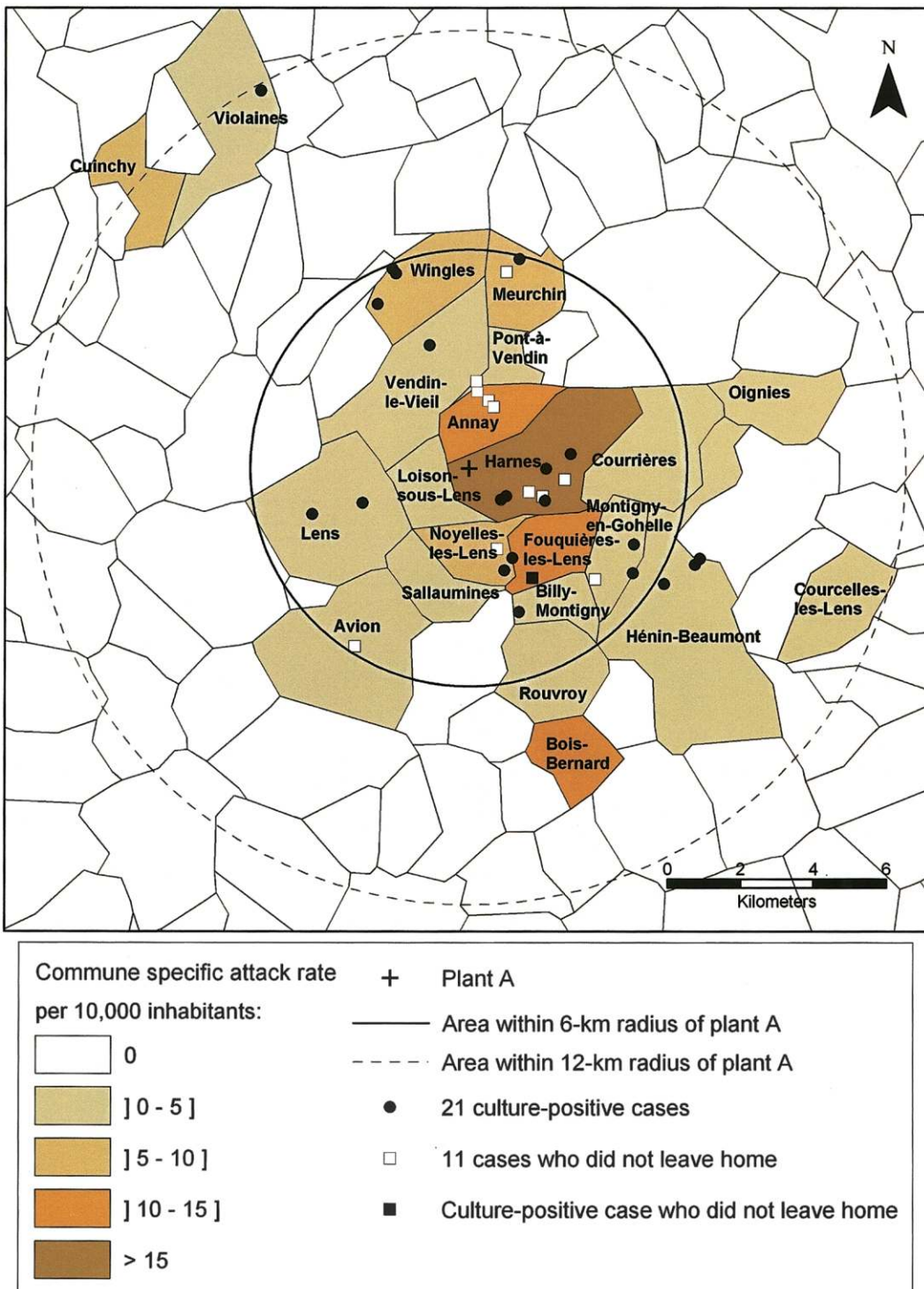


Figure 1. Cases of legionnaires disease ($n = 86$) by date of illness onset and date of intervention at plant A, Pas-de-Calais, France, November 2003–January 2004. CT, cooling tower.



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Figure 2. Commune-specific attack rates and geographical distribution of selected cases of legionnaires disease, Pas-de-Calais, France, November 2003–January 2004. Locations of cases’ homes are shown on the map. One culture-positive patient (not shown) lived farther from the area. Reprinted with permission from the Institut Géographique National.

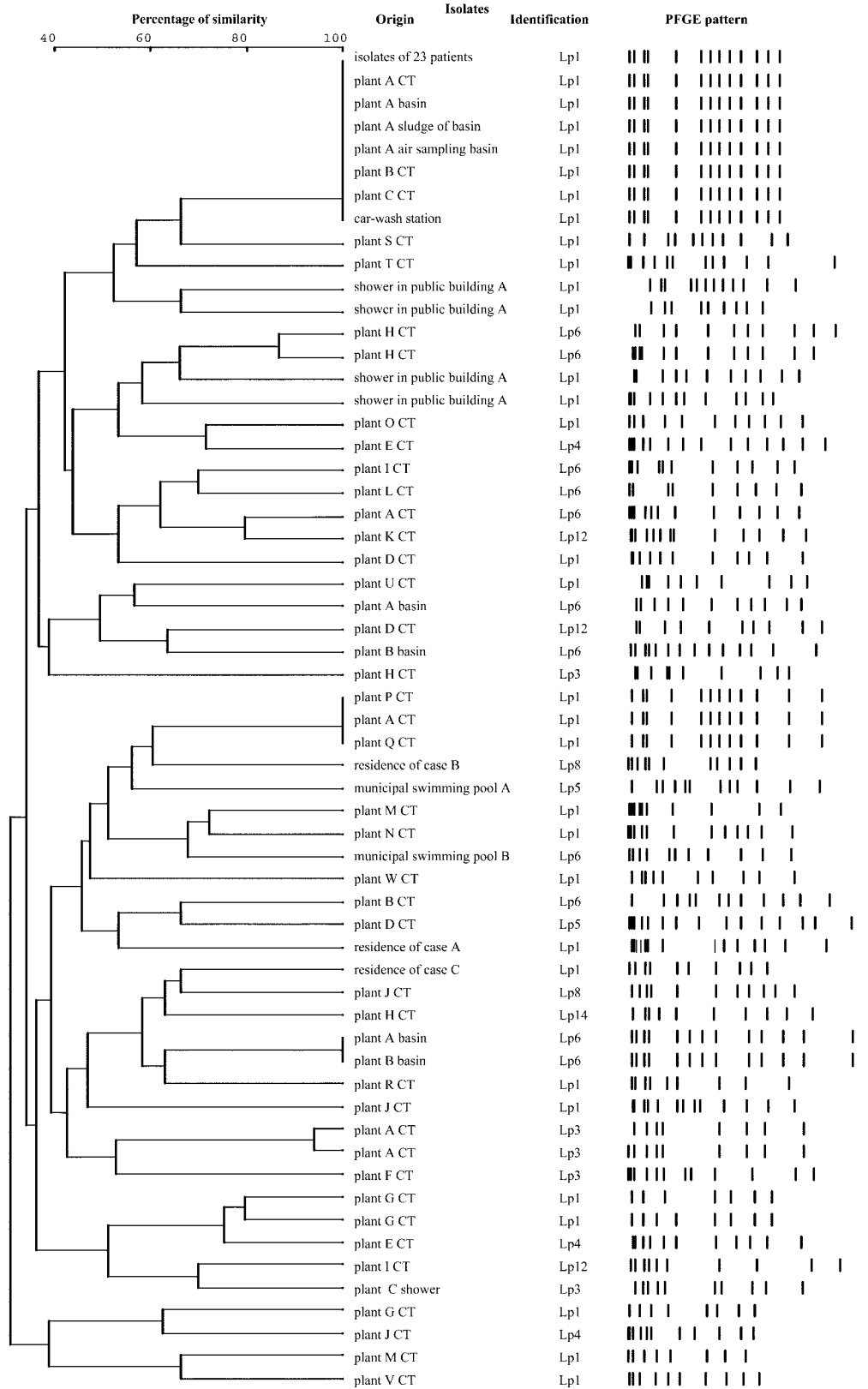


Figure 3. Schematic representation of pulsed-field gel electrophoresis (PFGE) patterns of 23 clinical *Legionella pneumophila* serogroup 1 (Lp-1) isolates and a selection of environmental Lp isolates. CT, cooling tower.

Table 2. Risk factors for legionnaires disease in commune residents, Pas-de-Calais, France, November 2003–January 2004.

Risk factor	Crude OR	Adjusted OR ^a (95% CI)	Cases exposed, %
Underlying medical condition or treatment ^b	1.3	1.4 (0.6–3.0)	74
Current smoking	2.1	2.7 (1.1–6.8)	22
Silicosis	2.8	3.6 (1.3–9.9)	22
>100 min spent outdoors daily	2.9	3.1 (1.1–9.0)	17

NOTE. Data are from the case-control study of 59 cases and 177 matched controls. CI, confidence interval; OR, odds ratio.

^a Obtained by conditional logistic-regression analysis and adjusted for all other covariates listed.

^b Included ≥ 1 of the following medical conditions or treatments: diabetes, chronic obstructive pulmonary disease, cardiovascular disease, renal disease, dialysis, transplantation, malignancy, chemotherapy, oxygen therapy, and use of corticosteroids.

medical conditions or treatments, silicosis, current smoking, heavy alcohol intake, living in a house, going out in the commune, having a car, and spending >100 min outdoors daily during the 10 days before the illness. In the final model, only smoking, silicosis, and spending >100 min outdoors daily increased the risk of LD significantly (table 2).

Environmental and microbiological investigation. The census identified 33 companies with 93 functioning CTs and 20 companies with other industrial cooling systems. Of >1100 environmental samples collected between 28 November and 15 February, 104 were culture positive for *Legionella*. For the following installations and sites, the numbers of positive/tested samples were as follows: CTs, 44/610; wastewater treatment plants, 43/97; cases' homes, 6/68; car-wash stations, 5/165; industrial cooling systems, 2/41; other installations capable of aerosol dissemination, 2/30; air samples in the vicinity of plant A, 2/12; municipal portable water systems, 0/36; wells and canals, 0/26; air conditioning systems in public buildings, 0/10; and decorative fountains, 0/6.

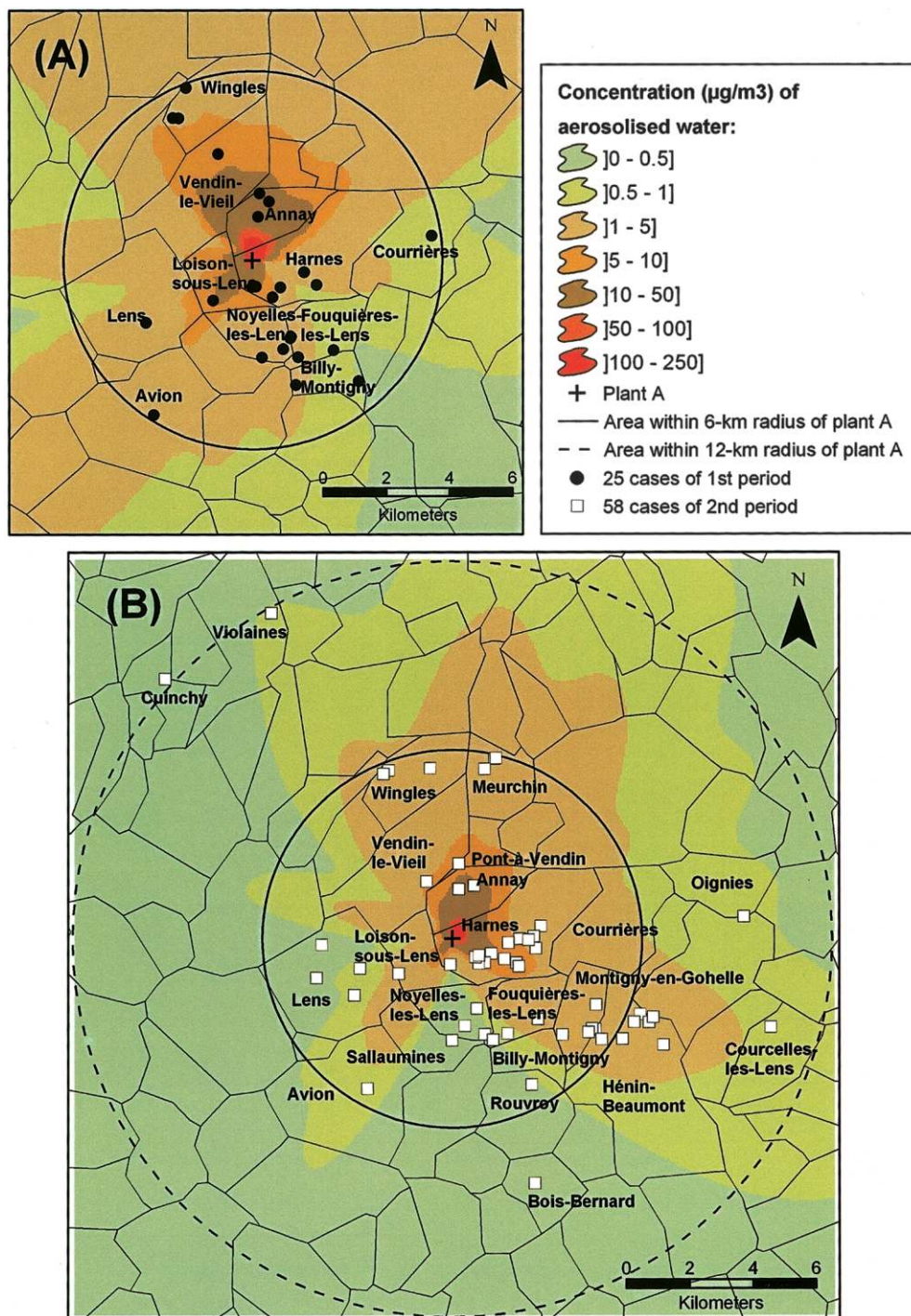
Of 260 environmental isolates identified as *Legionella*, 238 (92%) were *L. pneumophila*. A total of 125 Lp-1 isolates and 66 of 113 Lp serogroup 2–15 isolates were analyzed by PGFE. The subtyping results for these 191 (80%) environmental isolates showed that only 4 installations were contaminated with Lp-1 Lens: plant A, plant B, plant C, and a car-wash station (figure 3). In plant A, the epidemic strain was found in the CTs, in wastewater and sludge from the basin, and in the air in the vicinity of the basin (19 isolates in total). The level of contamination was high (10^6 – 10^{10} cfu/L) in plant A as well as in plant B. Plant B supplied biological sludge for the plant A waste basin and was located ~40 km away, in another district. In plant C and the car-wash station, both located in Harnes within 1 km of plant A, Lp-1 Lens was detected once (out of 18 and 5 samples, respectively) at the end of December and at low concentrations (100–1000 cfu/L).

Investigations at plant A. Plant A manufactured petrochemical solvents. It had 2 CTs, each 0–15 m high, occupying

a surface area of 2×125 m². With a capacity of 2×5800 kW, the CTs were capable of generating an amount of aerosols equal to 4300 L of water/day. The cooling circuits of CTs were interconnected and had a volume of 1200 m³, corresponding to several kilometers of pipes. Wastewater from the plant manufacturing process was treated by processing through collecting basins. The basin containing biological sludge was 2–3 m high, 4200 m² in area, equipped with aeration systems, and located ~300 m from the CTs.

The timing of control measures implemented at plant A are shown in figure 1. The environmental risk assessment concluded that (1) the cooling circuit configuration was highly prone to biofilm formation, making cleaning operations inadequate for elimination of *Legionella* bacteria; (2) high-pressure cleaning did not reach the entire CT contact surface and might have generated a large amount of contaminated aerosols; (3) CT restart created conditions that were particularly favorable for detaching *Legionella*-contaminated biofilm and airborne release; and (4) a considerable amount of *Legionella* bacteria in the wastewater basin of the plant might have become airborne in aerosol produced by surface ventilators, since air samples collected after final closure of the CTs and as far as ~300 m from the basin demonstrated Lp-1 Lens in aerosolized, respirable (≤ 5 μ m) water droplets.

Modeling results. The ADMS 3 model was run to simulate emissions from plant A during each wave of the outbreak. By use of different emission hypotheses, the model calculated concentrations of aerosolized water at target points and generated data mapping aerosol dispersions over the area of interest. During the first wave (figure 4A), the plume dispersion corresponded to a continuous CT emission, and the estimated mean concentrations of presumably contaminated aerosols were consistent with commune-specific attack rates, although the correlation was not statistically significant (table 3). During the second wave (figure 4B), the plume corresponded to emissions resulting from high-pressure cleaning and restart of the CTs. Although the plumes were substantially diluted beyond Harnes



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Figure 4. Atmospheric dispersion of aerosols and geographical distribution of cases during the first (A) and the second (B) waves of the legionnaires disease outbreak in Pas-de-Calais, France. The corresponding periods were 5 November–9 December 2003 and 11 December 2003–22 January 2004, respectively. Locations of cases' homes are shown on the map. Three patients (not shown) lived farther from the area. Reprinted with permission from the Institut Géographique National.

Table 3. Location, attack rate, and estimated mean concentration of aerosolized water per commune, according to the ADMS 3 model, during the first wave of the legionnaires disease outbreak, Pas-de-Calais, France, November–December 2003.

Commune	Distance, km (direction) ^a	Attack rate, cases/10,000 population	Aerosol concentration, ^b μg/m ³	
			20°C	15°C
Harnes-West	1.0 (S)	7.6	4.3	6.3
Annay	1.6 (N)	8.5	15.5	19.0
Harnes-East	2.0 (SE)	1.5	0.4	0.6
Noyelles-les-Lens	3.0 (S)	8.2	1.4	1.7
Lens	4.6 (SW)	0.3	0.8	1.0
Wingles	5.6 (NW)	3.5	3.3	3.8
Hénin-Beaumont	6.0 (SE)	0.4	0.1	0.3

^a Commune's distance and direction from plant A.

^b Mean water concentration in the plume when the emission temperature was 20°C or 15°C.

and the adjacent communes, the model showed good coverage of the communes where cases lived, and the coverage extended over a distance of at least 6 km from the plant.

DISCUSSION

A petrochemical plant with powerful industrial CTs was the most likely source of this large community-wide outbreak of LD. Several lines of evidence support this hypothesis. The attack rate was highest among residents of the commune in which the plant was located. CT operation and interventions at the plant were temporally associated with the outbreak. A single epidemic strain, Lp-1 Lens, was recovered from the CTs and wastewater basins of the plant and from air sampling of respirable droplets collected on the premises of the plant. Extensive environmental investigations identified 2 other installations located near the plant that were contaminated with Lp-1 Lens. Their positive samples were found late during the outbreak, however, and the low levels of colonization made them less likely to be sources of transmission. No other aerosol-producing installation was identified as a possible source in an area within a 12-km radius of the plant, and no evidence of potable water contamination or other source of indoor exposure was found. Furthermore, the temporal and geographical distribution of the 23 culture-positive cases supported the notion that there was 1 common persistent source of infection. In light of these findings, it seems unlikely that so many cases without close exposure to the plant would have acquired their infection from another unidentified source (or sources).

Unique in this outbreak was the large area within which exposure to *Legionella* bacteria apparently occurred. In 1989, Addiss et al. suggested a distance of airborne transmission of at least 1 to as many as 2 miles (3.2 km) from the contaminated CT [7], whereas other outbreak investigations have demon-

strated more limited distances [4–6]. In the present study, all cases lived in or visited an area within a 12-km radius of the plant without having frequented any places in common. Because most of the cases were elderly persons, their outdoor movements were restricted mainly to walking distances within their neighborhoods. Of the culture-positive patients, we were able to confirm 1 who lived 7 km from the plant and who did not come closer to the plant during the period of exposure, under the assumption of an incubation period of 2–10 days. Of the 12 patients who did not leave their home during the entire period of exposure, the most distant lived 6 km from the plant.

We attempted to simulate the atmospheric dispersion of presumably contaminated aerosols, using a classical Gaussian model. Because a number of physical and biological parameters—such as evaporation and coagulation of the simulated water droplets and survival and growth of *Legionella* bacteria in such atmospheric conditions and possibly within aerosolized amoebae [28]—are unknown, we could not quantify the actual concentrations of airborne *Legionella* bacteria in the plumes. Nevertheless, a good fit was obtained between the dispersion of the plumes simulated by the model and the geographical distribution of the cases, suggesting that extensive airborne transmission of *Legionella* bacteria over the epidemic zone was plausible. This notion was further supported by the results of the case-control study indicating that daily prolonged outdoor exposure was the only exposure-related risk factor.

Previous outbreak investigations have noted a temporal association with CT interventions, including changes in operation [3, 4, 7] and maintenance procedures [11]. In this outbreak, examination of the epidemic curve revealed a temporal association with various interventions at the plant. The first wave of the outbreak ended after the first CT closure. The second wave started during the period of high-pressure cleaning and peaked noticeably when the CTs were restarted. The outbreak began to phase out within 1 week after the final CT closure but was over only after the waste-basin ventilators were disconnected. These findings suggest that the CT cleaning operations and the waste-basin ventilation were direct sources of transmission. We are not able to assess their relative impacts, but our epidemiological and modeling results support the notion that these operations most likely played a role in the continuation and restart of the outbreak.

We can only hypothesize about why this outbreak occurred. The contaminated waste-basin sludge was traced back to its origin—an industrial site in another district—but no LD cases were detected there. Our identification of Lp-1 Lens in several environmental samples from the plant, before and after the cleaning operations, demonstrates that the bacteria can survive and proliferate in this industrial environment. A combination of the following events and conditions, among other factors yet un-

identified, was most likely critical in this outbreak: (1) an uninterrupted *Legionella* contamination from its ample reservoir in the wastewater basin; (2) a massive airborne release of *Legionella*-laden aerosols by the CTs; (3) inappropriate control measures, including hazardous high-pressure cleaning of the cooling system; and (4) meteorological conditions, together with the flat terrain, that particularly favored airborne dissemination of *Legionella*-laden respirable droplets over such a large area.

Widely reported risk factors for LD include advanced age, male sex, smoking, heavy alcohol intake, and chronic diseases associated with immunodeficiency [29]. Our case-control study attempted to identify other person- and exposure-related risk factors, to characterize the population at risk. The lack of significant association between LD and chronic diseases in our study, which has also been found in other outbreak investigations [10, 11], might be due to small numbers of cases and inaccurate self-reporting resulting in nondifferentiation of disease severity. On the contrary, silicosis, a previously unknown risk factor, was found to be strongly associated with LD in our study. Information bias related to this outcome is probably negligible, since this occupational lung disease of coal miners is well screened by health insurance providers and is known by the population, which lives in an ancient coal-mining area.

The attack rate for residents of the affected area was relatively low in this outbreak, as in previous community outbreaks of LD [7, 9, 10]. The low attack rate could be due to host factors, but differences in exposure might play a role. O'Brien and Bhopal postulated that inhaling *Legionella*-laden amoebae rather than the bacteria alone might cause LD [30]. Thus, only a few random individuals inhale enough amoebae, whereas others escape by not inhaling the dose required to cause illness. This might, in part, explain the inconsistent results between previous studies regarding the risk associated with components of an exposure dose (i.e., duration of exposure, frequency of exposure, and distance from the source) [9, 11]. In the present study, we could not demonstrate a dose-response effect between outdoor exposure and the likelihood of having LD or identify other risk factors from a wide range of exposures.

In the past few years, several large community outbreaks of LD occurred around the world [10, 11, 18]. Compared with these outbreaks, one of the striking features of the present outbreak is the high case fatality rate (21% vs. 1.1%–11%). It is possible that differences in host factors account for this difference in mortality. Another intriguing possibility is that the pathogenicity of the strain played a role. Because the outbreak occurred during the winter months, when outdoor temperatures rarely exceeded 10°C, and the majority of cases were infected several kilometers from the source, suggesting a low dose of inoculum, the strain incriminated in the present outbreak may have been unusually resistant and virulent. This notion is consistent with the results of a comparative genomic study by Cazalet et al., which showed

a high level of variation between Lp-1 Lens and the predominant endemic strain in France [27].

In France, since the reinforcement of the policy of national mandatory notification of LD in 1997, case reporting has improved considerably [20], and community outbreaks have been detected more frequently and in a more timely manner. During the past 5 years, there have been 10 small community outbreaks in which CTs were implicated as the most likely sources of contamination. Although most of the LD cases reported in France still remain sporadic and have no epidemiological link to an identified source, a recent ecological study conducted in France suggested that any industrial systems generating aerosols could be potential sources of contamination for sporadic LD cases [31]. After the present outbreak, the national authorities issued new regulations concerning the installation and maintenance of CTs [32], as well as guidelines for the investigation and management of risk related to *Legionella* bacteria [33].

In conclusion, this large outbreak of LD in Pas-de-Calais provides additional evidence of long-distance airborne transmission of LD. The circumstances of this outbreak were unusual. Powerful industrial CTs, ineffective and hazardous control measures, and extensive environmental contamination of an industrial site together resulted in a community-wide outbreak of LD in which airborne transmission of *Legionella* bacteria appears to have extended over a distance of at least 6 km from the source. Should further studies confirm this finding, it will have major public-health implications for the control and prevention of LD.

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