

Repeat capture–recapture studies as part of the evaluation of the surveillance of Legionnaires' disease in France

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SUMMARY

We evaluated improvements made to the mandatory notification surveillance system for Legionnaires' disease in France by estimating its sensitivity in 1995 and 1998 using a repeat capture–recapture method. A case of Legionnaires' disease was defined as a person treated for pneumonia in whom legionella had been detected. Patient details were collected from (1) mandatory notifications; (2) the National Reference Centre for *Legionella*; (3) a postal survey of all hospital laboratories. The three sources were cross-matched and 715 individual cases were identified. A log-linear model, which included an interaction term between mandatory notifications and both the National Reference Centre and Laboratory sources, provided an estimated total of 1124 cases (95% CI 973–1275) in 1998, a twofold increase compared with 1995. The sensitivity of the surveillance system improved from 10% in 1995 to 33% (95% CI 29–38%) in 1998. Capture–recapture methods are important tools in the evaluation of surveillance systems.

INTRODUCTION

Legionnaires' disease is a bacterial pneumonia, acquired through the environment, which is classically associated with explosive outbreaks [1, 2]. However, the main burden of disease is linked to sporadic cases for which the source of infection is rarely identified [3, 4]. The recognition of outbreaks or clusters of Legionnaires' disease will provoke a public health investigation in order to implement appropriate control measures; such measures are also carried out for single cases of hospital-acquired infection [5, 6]. Thus, the surveillance systems for Legionnaires' disease need to be sensitive in order to detect such outbreaks, especially as clusters are often small, and may be both temporally and geographically disparate [4, 7].

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In France, the surveillance of Legionnaires' disease is based on the mandatory notifications of clinical cases as well as a voluntary laboratory reporting system operated by the National Reference Centre. A capture–recapture study in 1995 estimated the sensitivity of the mandatory notification system to be 10% [8]. As a consequence, a number of measures were introduced in 1997 to improve the system of mandatory notifications of which the most important was an improved reconciliation between the mandatory notification and laboratory surveillance systems [5].

Capture–recapture methods were first developed to enumerate wild animal populations [9]. More recently, these methods have been applied to epidemiology and are now increasingly employed in public health medicine to estimate the burden of diseases [10] and social conditions [11], to assess the sensitivity of case reporting within surveillance systems and

disease registries [12, 13] and to evaluate the impact of interventions [14].

The aim of this study was to estimate the total number of cases of Legionnaires' disease diagnosed in France in 1998 and thus the sensitivity of the mandatory notification surveillance system. Three sources of data were used in a capture-recapture study to estimate the burden of disease in 1998 and compared with the results of a study conducted in 1995, which used similar methods and sources. Both the evolution in the incidence of diagnosed cases of the Legionnaires' disease and the improvement in the sensitivity of the mandatory notification surveillance system after the implementation of the measures in 1997 are reported here.

METHODS

Case definition

The case definition for Legionnaires' disease was similar to that used by the European Working Group for Legionella Infections [7]. The definition was a person, resident in mainland France, who had been diagnosed in 1998 with a pneumonia and in whom *Legionella* spp. had been detected by culture, by a positive urinary antigen test, or by a sero-conversion defined as fourfold rise in antibody titre with a second titre ≥ 128 (confirmed case) or by a single elevated antibody titre of ≥ 256 (probable case).

Sources

The following three sources of data were used to collect information on cases of Legionnaires' disease in France in 1998:

Mandatory Notifications (MN): Legionnaires' disease became a mandatory notifiable disease in 1987. Treating physicians report all cases to the district public health department and this information is then sent to the Institut de Veille Sanitaire (InVS) using a standardized data collection form. Information for this study including first name, initial of surname, date of birth (or age), sex, department of residence, date of onset of illness and diagnostic results was obtained directly from the database held at the InVS.

National Reference Centre (NRC): laboratory surveillance of Legionnaires' disease is undertaken by the NRC which receives samples on a voluntary basis from laboratories throughout France for either typing

or confirmation of diagnosis. For each case of Legionnaires' disease recorded by the NRC, information was collected on first name, initial of surname, date of birth (or age), sex, department of residence, date the sample was taken and diagnostic results.

Laboratories (LAB): a postal survey of hospital and private laboratories was conducted. A first letter was sent to 415 laboratories in April 1999 and a reminder letter was sent at the end of May 1999. A total of 289 laboratories (69%) responded to the survey by providing information on the types of diagnostic tests used and the number of requests received. For each case of Legionnaires' disease diagnosed by the laboratory, information was collected on first name, initial of surname, date of birth (or age), sex, department of residence, date the sample was taken and diagnostic results.

Identification of duplicate cases

The same definition of either confirmed or probable cases was applied to lists from the three sources of data. Epi-Info 6 statistical software (Centers for Disease Control, Atlanta, Georgia, USA) was used to identify duplicates, those within each source (intra-source duplicates) were eliminated, whilst those between sources (inter-source duplicates) were recorded and used in the capture-recapture analysis.

In order to identify intra- and inter-source duplicate cases, a code of the initial of the surname, first three letters of the first name, age in years and sex was constructed. Duplicate cases were those records with the same code as well as dates of birth, date of illness and the department of residence. A more sensitive algorithm was used to identify further duplicates by linking those records that did not have an identical code because of one of the following: a difference in age due to a one figure change in date of birth or illness, a different or missing first name or a missing or different sex.

Capture-recapture analysis

In using capture-recapture methods, independence of sources (the probability of being declared in one source is unaffected by being declared in a second source) and heterogeneity of capture (characteristics of a case will alter its probability of appearing in a source) can be controlled for by using log-linear modelling with more than two sources thereby to

Table 1. Cases of Legionnaires' disease by source of capture and characteristics of case

Sources*	NRC†	+	+	+	+	-	-	-	Total
	MN‡	+	+	-	-	+	+	-	
	LAB§	+	-	+	-	+	-	+	
Not stratified:		95	77	52	132	105	93	161	715
Region:	Ile-De-France	18	8	7	12	34	12	70	161
	Rhône-Alpes	21	41	4	71	6	17	9	169
	Rest of France	56	56	41	47	37	63	82	382
Diagnostic method:	Confirmed cases	91	96	25	56	65	71	75	479
	Culture	56	28	15	13	11	12	10	145
	Urinary antigen	15	36	4	10	34	24	28	151
	Seroconversion	20	32	6	33	20	35	37	183
	Probable cases (single high titre)	4	9	27	74	12	21	86	233

* +, present in source; -, not present in source.
 † NRC, National Reference Centre.
 ‡ MN, mandatory notifications.
 § LAB, laboratory survey.
 || Confirmed cases are only those diagnosed by culture, urinary antigen test or seroconversion.

obtain an unbiased estimate of the total population [15, 16]. In order to control for heterogeneity of capture, data were stratified by the selected variable and estimates were obtained in each stratum of data [17–19].

Statistical analyses were performed using the 4F programme in the BDMP software package (BDMP statistical software Inc, Los Angeles). A backward stepwise procedure was used in the modelling, where starting from the saturated model, interaction terms were removed until the model resulted in a poor fit, evaluated by the maximum likelihood ratio (G^2), between the expected and observed data [16].

The final model was selected as the one with least number of terms and statistical best fit as judged by using the maximum likelihood ratio statistic (G^2) and the Bayesian Information Criterion [$BIC = G^2 - (\log N_{OBS}/2\pi)df$] where df represents the degrees of freedom of the model and N_{OBS} is the number of observed cases. The final model was selected on the basis of the lowest BIC values as this criterion favoured the model with the lowest G^2 , while penalizing those with increasing numbers of parameters in the model. The weighted average of the BIC estimates was calculated only for those models with a negative BIC value, as a positive value indicated a poor statistical fit [20]. The 95% confidence intervals (95% CI) were calculated using variance equations for the selected model identified in the log-linear modelling [9, 21].

We stratified the data by region of report and by method of diagnosis, as in 1995 these were identified as variables with heterogeneity of capture [8]. For region of report, France was divided into three: Ile-de-France, the most populous region of France including Paris; Rhône-Alpes includes Lyon where the NRC is based, and the rest of France. Cases were assigned according to the case definition above employing a hierarchy of diagnostic method in which culture > urinary antigen > seroconversion > single elevated titre. Sensitivity of a source was calculated using the number of observed cases (N_{OBS}) divided by the estimated number of cases (N_{EST}), the 95% CI by dividing N_{OBS} by the upper and lower estimates of the population.

Ethical approval

Ethical approval was sought and obtained from the Commission Nationale de l'Informatique et des Libertés (CNIL), the national responsible body.

RESULTS

The three sources yielded a total of 1152 records with 715 individual records identified by cross-matching, of which 95 were common to all three sources, 234 were common to two sources and 406 were unique to one source (Table 1). Nearly a quarter of these

Table 2. Estimated numbers of cases of Legionnaires' disease and statistics for each possible model obtained by log-linear modelling of all cases, France, 1998

Model*	Degrees of freedom	Maximum likelihood ratio	<i>P</i>	Aikake Information Criteria	Bayesian Information Criteria	Total estimated number of cases	Estimated number of cases	Total estimated number of cases ($N_{OBS} + x$) (95% CI)
$M \times N, L \times N, M \times L$	0	0.00	1.00	0.0	0.0	715	447	1162 (915–1408)
$M \times N, L \times N$	1	15.18	0.00	13.2	8.1	715	194	909 (838–981)
$M \times L, M \times N$	1	0.18	0.67	–1.8	–6.8	715	409	1124 (973–1275)
$N \times L, L \times M$	1	35.86	0.00	36.9	30.8	715	117	832 (788–876)
$M \times N, L$	2	17.57	0.00	13.6	3.5	715	237	952 (890–1014)
$L \times M, N$	2	50.39	0.00	46.4	36.3	715	173	888 (840–937)
$N \times L, M$	2	38.69	0.00	34.6	24.6	715	116	831 (794–867)
M, N, L	3	52.28	0.00	46.3	31.2	715	184	899 (802–996)
Weighted estimate								1123

* M, Mandatory notifications; N, National Reference Centre; L, Laboratories.

records were reported from the Ile-de France (23%) and from Rhones-Alpes (24%) respectively and the remainder (53%) from the rest of France. The majority of records (67%) were confirmed cases of which 20% were confirmed by culture, 21% by urinary antigen testing and 26% by seroconversion (Table 1). The remaining 33% of records were defined as probable cases as they had been diagnosed by a single high antibody titre.

The same laboratories were surveyed in the 1998 survey as those in 1995 and the response rate recorded in 1998 (69%) was higher than that observed in 1995 (261/432, 60%, $\chi^2=8.05$, $P<0.005$). Of the laboratories surveyed in 1998, 122 (42%) practised at least one diagnostic method for Legionnaires' disease, a similar proportion to that observed in 1995 (38%). A third of laboratories used culture (34%) and 23% used serological methods to diagnose Legionnaires' disease. Forty laboratories (14%) used urinary antigen testing in 1998 and a further 65 planned to introduce the test in 1999.

The estimated numbers of cases and the statistics for each model obtained by log-linear modelling are presented in Table 2. The selected model ($M \times N$, $M \times L$) demonstrated a good fit with the observed data ($P=0.67$), had a negative BIC (–6.8) and included dependence between the mandatory notification and both the National Reference Centre and the laboratory sources. This model estimated that the total number of diagnosed cases of Legionnaires' disease in France in 1998 was 1124 (95% CI 973, 1275). The less sensitive algorithm identified 25 more individual records (740 vs. 715 cases) and the same model estimated the total number of cases in 1998 to have been

1190 (95% CI; 1026–1354), 6% greater (or 66 more) than when using the more sensitive algorithm to identify duplicates.

Log-linear modelling was performed in each of the strata of region and diagnostic test and all the selected models exhibited a good statistical fit with the observed data ($P>0.05$) and negative BIC values (Table 3). The total estimates of the population obtained by summing the estimates for each of the strata of either region (1094; 95% CI 745–1441), case status (i.e. confirmed or probable; 1073; 95% CI 866–1280), or diagnostic test (1128; 95% CI 780–1284) were all within 5% of the estimate obtained for non-stratified cases (Table 3).

There was no significant difference in the estimated sensitivity of the three sources (Table 3). When the data were stratified by region (Table 3), the sensitivity of the mandatory notification source was highest in the rest of France (44%), that of the NRC source in Rhône-Alpes (42%) and that of the laboratory source in Ile-de-France (56%). For each of the three sources, the sensitivity was greater for confirmed (diagnosed by culture, urinary antigen or seroconversion) than for probable cases diagnosed by a single elevated titre of antibody (Table 3). Furthermore, for all three sources, the sensitivity of cases diagnosed by culture was higher than by all other diagnostic methods (Table 3).

The number of cases of Legionnaires' disease reported to the mandatory notification system increased sevenfold between 1995 and 1998, from 51 to 370 (Table 4). A twofold increase in the estimates obtained from the respective capture-recapture studies was observed, from 524 in 1995 to 1124 in 1998

Table 3. Selected models with statistics and the estimates of the number of cases of Legionnaires' disease and sensitivity of each of the three sources for all cases and stratified by either region or by diagnostic test, France, 1998

	Model*	P	Maximum likelihood ratio	Bayesian Information Criteria	Total estimated number of cases (95% CI)	% Sensitivity (95% CI)		
						Mandatory notifications	National Reference Centre	Laboratories
Not stratified	M × N, M × L	0.67	0.18	-6.8	1124 (973-1275)	33 (29-38)	34 (30-39)	34 (30-40)
Stratified by Region								
Ile-de-France	M × N, M × L	0.67	0.18	-6.4	281 (164-398)	26 (18-44)	16 (11-26)	56 (32-75)
Rhône-Alpes	M × N, M × L	0.49	0.48	-6.1	329 (135-522)	26 (16-68)	42 (26-100)	12 (8-80)
Rest of France	M × N, L	0.06	7.25	-9.4	484 (446-521)	44 (41-48)	41 (38-45)	45 (41-48)
Stratified by diagnostic test								
Confirmed†	M × N, M × L	0.83	0.05	-6.6	656 (562-750)	49 (43-58)	41 (36-48)	39 (34-46)
Culture	M, N, L	0.08	6.67	-13.2	151 (123-179)	71 (60-87)	75 (64-93)	61 (51-75)
Urinary antigen	M × N, N × L	0.95	0.00	-6.6	173 (157-188)	63 (58-70)	38 (34-41)	47 (43-52)
Seroconversion	M × N, M × L	0.83	0.05	-6.6	387 (196-387)	28 (19-55)	24 (16-28)	21 (14-42)
Probable (single high titre)	M, N, L	0.75	1.23	-18.7	417 (304-530)	11 (9-15)	27 (21-38)	31 (24-42)

* M, Mandatory notifications; N, National Reference Centre; L, Laboratories.

† Confirmed cases are only those diagnosed by culture, urinary antigen test or sero-conversion.

(Table 4), respectively an incidence of 0.9 and 1.9 per 100 000 of the population. The estimated sensitivity of the mandatory notification system increased three-fold, from 10% in 1995 to 33% in 1998. The improvement in the sensitivity of the mandatory notification system was noted in all three regions of France as well as for all types of diagnostic methods (Table 4).

DISCUSSION

To the best of our knowledge, this paper describes the first report of a repeat capture recapture study, the results of which can be used to monitor changes in disease incidence and to evaluate improvements in disease surveillance systems. In France, between 1995 and 1998, there was a twofold increase in the estimated incidence of Legionnaires' disease and a threefold increase in the sensitivity of the mandatory notification system. Estimates of the total number of Legionnaire's cases obtained in the two studies were comparable as the same methods and sources were used.

The increase in both the estimated incidence and the number of cases reported to the mandatory notification system was probably due to a combination of improved diagnosis and reporting of Legionnaires' disease by clinicians. It has long been recognized that physicians both under-diagnose [22, 23] and under-report [8] Legionnaires' disease. However, the introduction of urinary antigen testing has improved both the diagnosis [24] and reporting of the disease to the public health authorities [25]. In France, urinary antigen testing only became widespread in the period between these two studies, and the use of this diagnostic tool may account for the increase in estimated incidence and improved reporting of Legionnaires' disease. However, the doubling of incidence may be due in part to an increase in the burden of disease, although we can find no plausible explanation for such a large and rapid phenomenon.

Before 1997, the mandatory notification system had only detected nosocomial outbreaks of Legionnaires' disease [5], although subsequent improvements appeared to have had some impact as it has since played an important role in the identification of a number of community outbreaks of Legionnaires' disease [26-28]. Nonetheless, one of the objectives of surveillance system for Legionnaires' disease is the early detection of epidemics [6]. An overall sensitivity of only 33% is probably too low and many smaller community outbreaks of Legionnaires' disease may still be missed. A number of improvements to the surveillance of

Table 4. Estimated numbers of cases of Legionnaires' disease, the number reported and the estimated sensitivity of the mandatory notification, stratified by either region or diagnostic test, in France in 1995 and 1998

	1995			1998		
	Number reported	Number estimated	Sensitivity (95% CI)	Number reported	Number estimated	Sensitivity (95% CI)
All cases	51	524	10 (9–11)	370	1124	33 (29–38)
Stratified by Region						
Ile-de-France	4	155	3 (1–7)	72	228	26 (18–44)
Rhône-Alpes	3	88	3 (1–7)	85	228	26 (16–68)
Rest of France	44	289	15 (11–20)	210	533	44 (41–48)
Stratified by diagnostic test						
Confirmed*	37	289	13 (12–14)	324	568	49 (43–58)
Culture	19	83	23 (22–24)	107	150	71 (60–87)
Urinary antigen	—	—	—	110	175	63 (58–70)
Seroconversion	18	206	9 (8–9)	107	243	28 (19–55)
Probable (single high titre)	13	235	6 (5–6)	46	421	11 (9–15)

* Confirmed cases are only those diagnosed by culture, urinary antigen test or seroconversion.

Legionnaires' disease in France are now being considered including closer collaboration between the InVS and laboratories, enhancing the national training role of the NRC and encouraging the introduction of urinary antigen testing in more hospital laboratories in France.

The dependence between the NRC and the mandatory notification system, co-ordinated by the InVS, was expected as since 1997 there has been a close collaboration between the two institutes. Laboratories that send samples to the NRC are encouraged also to report cases of Legionnaires' disease to the InVS. This collaboration may explain the interaction between the mandatory notification system and laboratory sources and could have obscured a possible interaction between the laboratory and NRC sources. Thus, an interaction may have existed between the three sources used in this study, although this cannot be tested using log-linear modelling as there is an assumption of a maximum of $k - 1$ interactions, where k is the number of sources [9, 29].

Heterogeneity of capture can be controlled for by stratification of the data [17–19], and, by obtaining estimates for each of the strata, the representativeness of each of the sources can be assessed [13]. The higher sensitivity of the NRC source amongst cases from the Rhône-Alpes region was expected as the NRC is based in Lyon. Similarly, the increased sensitivity of the laboratory source amongst cases from the Ile-de-France region could be due in part to the existence of a strong network of expert microbiologists in Paris. The higher sensitivity of confirmed cases was also noted

in France in 1995 [8]. The improved sensitivity for detection of cases diagnosed by culture may be because isolates are sent to the NRC which encourages notification; improved notification has been reported for cases diagnosed by urinary antigen testing [25].

An important assumption of capture-recapture methods is that all cases are accurately diagnosed. However, this condition may not have been met for probable cases due to the low specificity and low positive predictive value, estimated to be 15%, of a single high antibody titre for a diagnosis of Legionnaires' disease [24, 30]. This will have resulted in an over-estimation of the total population and thus an under-estimation of sensitivity of the sources and may explain partly why the lowest sensitivity of all three sources was noted for probable cases.

The accurate identification of all duplicate cases, both within and between sources, is a difficulty encountered in many capture recapture studies [9, 29]. Personal details are often unavailable and thus records must be linked using an algorithm and common set of covariates. If the definition of a duplicate case is too specific, the population will be over-estimated, and if too sensitive, it will be under-estimated [31]. It has been proposed that algorithms of varying sensitivity should be used to match records and the estimates compared [17]. When the less sensitive algorithm for the identification of duplicates was employed, we observed only a small increase in the total estimate of the population, demonstrating that the chosen, and more sensitive, algorithm may have only slightly under-estimated the total population.

In capture recapture methods, the sources employed must collect data for the same geographic region and time period. Only information on cases of Legionnaires' disease resident in France was collected from the three sources. However, the mandatory notification source collected information on cases by date of first symptoms whereas the other two sources included cases by date of first sample. Thus, cases that occurred at the end of 1998 may have been declared in the mandatory notifications, but not by the other two sources. However, as the incubation period of Legionnaires' disease is short (2–10 days) [22], this probably had only a minor effect on the estimations.

The use of capture recapture methods is an attractive alternative to longer and more costly methods to determine the sensitivity of surveillance systems – an important component in their evaluation. Furthermore, the repetition of these studies permits the evolution of the incidence of the diagnosed disease and the sensitivity of the surveillance system to be monitored, as well as assessing the impact of any improvements requiring to be made to the system. For a surveillance system for Legionnaires' disease to be able to identify outbreaks or grouped cases, not only must there be timely reporting of cases but the system must also have good sensitivity. Though we estimated that the sensitivity of the mandatory notification surveillance system in France had improved significantly, in order for it to achieve its objectives, further improvements are needed.

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