Legionnaires' disease in the Netherlands, 1998-2006

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CHAPTER FOUR

Use of surface water in drinking water production associated with municipal Legionnaires’ disease incidence

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ABSTRACT

Study objectives. Given an observed geographical variation in Legionnaires’ disease (LD) incidence in the Netherlands, the aim of the study was to test the hypothesis that type of drinking water production was an independent determinant of Legionnaires’ disease incidence.

Design. For the 1987–2005 period, the incidence of LD in the Netherlands and the price of water as a proxy for production type was studied at the municipal level. The data on price of water were available at the municipal level.

Methods. For each of the 466 municipalities in the Netherlands a mean standardised incidence rate per 100,000 inhabitants over the 1987–2005 period was calculated, excluding patients with most probable source of infection abroad or in hospital. Logistic regression was used to assess the relation of price of water to the incidence rates. In order to diminish bias, diagnostic and inclusion bias were estimated using questionnaire data collected from all 62 medical microbiology laboratories in the country.

Main results. The incidence of LD varied between municipalities from 0.0 to 5.6 per 100,000 inhabitants per year. In univariate analysis high versus low water price was positively associated with high municipal incidence rate (odds ratio 1.9; 95% confidence interval 1.5 – 2.6). The association persisted (odds ratio 5.1; confidence interval 3.2 – 8.0) after correction for diagnostic and inclusion bias.

Conclusions. Price of water as proxy for type of water production was an independent risk factor for high municipal LD incidence in the Netherlands. This can guide future prevention policies.

Key words. Legionnaires’ disease, pneumonia, incidence, public health, environmental exposure

INTRODUCTION

Legionnaires’ disease (LD) is an acute pneumonia of low incidence [1,2] which was first described after a large outbreak in Philadelphia in 1976 among visitors of a legionnaires’ convention held in a hotel, and passers-by at the same hotel. [3] The outbreak was shown to be caused by a newly discovered genus named Legionella. [4] To date, 49 Legionella species have been identified [5] many of which are ubiquitous in (manmade) aquatic environments. Legionella pneumophila which is the predominant species isolated from LD patients consists
of 15 serogroups, of which serogroup 1 is the most common, followed by serogroups 4 and 6. [6] In the USA, 91% of isolates from Legionnaires’ disease patients are typed as *Legionella pneumophila* serogroup 1. [6] The gram-negative bacilli are capable of infecting humans by aerosol inhalation or by drinking and subsequent aspiration of water. Given these modes of transmission, prevention efforts have focused on aerosol-producing plants and devices [7,8,9,10] and the presence of *Legionella* species in water installations in large buildings like hotels [11,12] and hospitals. [13,14]

Less attention has been given to the initial contamination of water installations by the drinking water delivered by water companies and the preceding water production process. We assume that *Legionella* infection of humans follows contamination and subsequent colonisation of water systems as a result of drinking water supplied with low to undetectable concentrations of *Legionella*. In the Netherlands a substantial part of the drinking water is produced from surface water. This raw material is known to be the natural habitat for *Legionella*, [15] and might lead more often to contamination of water installations when compared to production with groundwater. In the Netherlands the drinking water is and has always been distributed without disinfectants. After the 1999 outbreak the Dutch Health Council, asked for an update on *Legionella* prevention, explicitly advised against residual disinfection of municipal drinking water and the Dutch government opted accordingly. [16]

As large differences in LD incidence between provinces in the Netherlands have been observed in the past, [17] we investigated if these differences coincided with geographic differences in the origin of drinking water (ground water or surface water), using the price of water as a proxy. Therefore, we conducted an incidence study at a more detailed level than the province: the municipality. In order to reduce the influence of demographic differences at community level we corrected for age and gender. Furthermore, we assessed potential confounding related to diagnostic and inclusion bias by estimating underdiagnosis and underreporting at laboratory level and subsequently corrected for these factors in a multiple logistic regression model.

### Methods

**Inclusion of patients**

Legionnaires’ disease (LD) is a notifiable disease in the Netherlands since July 1, 1987. Treating physicians report LD patients within 24 hours to one of the 38 Regional Public Health Services (RPHS) in the country. Public health physicians based at the RPHS subsequently report confirmed and probable LD patients within 24 hours to the Ministry of Health. For our study we included all LD patients who had been notified from July 1, 1987 through December 31, 2005, with the exception of 188 patients who were part of a large outbreak in 1999. This outbreak resulted from a contaminated and inappropriately disinfected whirlpool which was on display and functioning for ten days. The water temperature was kept at 37 degrees Celsius and the water was not refreshed. Since the whirlpool was close to the entrance of a large hall a total of 77,000 visitors passed by. [18]
Subsequently, as we aimed to explore geographical difference in the Netherlands, we excluded LD patients who stayed abroad or stayed in a hospital during five or more days of their incubation period. We defined a confirmed case of LD as a patient suffering from symptoms compatible with pneumonia, with radiological signs of infiltration, and with laboratory evidence of *Legionella* spp. infection. Laboratory evidence included isolation of *Legionella* spp. from respiratory secretions or lung tissue, detection of *L. pneumophila* antigens in urine, seroconversion or a fourfold or higher rise in antibody titres to *L. pneumophila* in paired acute- and convalescent-phase sera. We defined a probable case of LD as a patient suffering from symptoms compatible with pneumonia, with radiological signs of infiltration, and with laboratory findings suggestive of *Legionella* spp. infection. These findings included a high antibody titre to *L. pneumophila* in a single serum, direct fluorescent antibody staining of the organism and detection of *Legionella* species DNA by polymerase chain reaction in respiratory secretions or lung tissue.

**Calculation of municipal LD incidence rates**

The incidence was studied previously at the provincial level. [17] The next administrative unit in the Netherlands is the municipality. Based on the LD notification data collected in the 1987–2005 period, for each of the 466 municipalities in the Netherlands a mean yearly LD incidence rate per 100,000 inhabitants was calculated and adjusted for age and gender by direct standardisation using the January 1, 1996 census. In order to minimise bias due to misclassification of the origin of infection, for each LD patient the place of residence was used as a proxy for source of infection, unless:

- A patient was part of a cluster or outbreak with an identified source of infection. Then the case was attributed to the municipality where the source of infection was situated.
- A patient had stayed away from home in a different community for five or more days during the incubation period (2–10 days). Then the case was attributed to the non-residential municipality.

**Diagnostic and inclusion bias**

In order to assess the impact of diagnostic and inclusion bias on differences in LD notifications in August 1998, 167 questionnaires were sent to all registered medical microbiologists working in 62 different hospital-based laboratories in the Netherlands. In February 1999, non-responders were resent the questionnaire. Topics covered in this questionnaire concerned the types of LD diagnostic assays used in the laboratory. Since it was expected that a large outbreak in 1999 in the Netherlands [18] would influence laboratory practice, new questionnaires were sent in August 2002 and for non-responders again in March 2003. Added topics in the new questionnaire concerned the region of adherence and the total number of requests for *Legionella* diagnostics in the years 2000 and 2001. Furthermore, an overview of diagnosed LD patients was asked for the years 2000 and 2001. Several variables were inferred from the questionnaires data. As indicators of diagnostic bias, diagnostic activity was calculated by dividing the number of requested tests by the number of inhabitants of the region of adhe-
rence in the years 2000 and 2001. Also, the ratio of positive tests to requested tests and the ratio of notification after the 1999 outbreak to before 1999 were calculated. As an estimate for inclusion bias, LD underreporting was calculated as a ratio of non-notified to notified LD patients in the years 2000 and 2001. To estimate the effect of the 1999 outbreak, for each province a ratio of notified LD before and after 1999 was calculated. Each of the variables was dichotomised using the mean as discriminating value.

Risk factors

Ideally, as our basic hypothesis was that geographical differences in LD incidence are a result of differences in the initial contamination of drinking water at delivery, we would have used data on *Legionella* contamination of the drinking water supply. Since 2004, water companies in the Netherlands are obliged to report contamination of *Legionella* in their distribution system to the Ministry of the Environment. In that year, none of 371 sampling points were reported to be contaminated with *Legionella pneumophila* and only twelve (3.2%) with other *Legionella* species. [19] Other than that, systematically collected data on contamination of drinking water with *Legionella* species in the Netherlands have not been published. A report on the contamination of the water distribution system in the Netherlands with *Escherichia coli* covering a ten-year period has been published. [20] Unfortunately, since there is no correlation between the presence of *E. coli* and *Legionella* species in drinking water, [21] these data could not be used for our study either. Therefore, we hypothesised that differences in raw material used for the production of drinking water would lead to (undetectable) differences in contamination. We used the 2004 price of 1,000 litres of water as a proxy for the raw material used in the production process of the water delivered. [22] In general, higher prices result from more intensive production processes using surface water as raw material. [23] Conversely, use of groundwater leads to lower prices. The variable "price of water" was dichotomised using the mean price of water as the discriminatory value.
Statistical analysis

Statistical analysis was performed with version 14.0 of the SPSS statistical program (Statistical Product and Service Solutions, Chicago, Illinois, U.S.A.). Univariate analysis was used to estimate the association between municipal incidence of Legionnaires’ disease and price of water. In a multiple logistic regression model using stepwise backward elimination the association was corrected for the factors described above. Variables were retained in the model if the likelihood ratio test was significant (p<0.1).

RESULTS

Patient selection

From 1 July 1987 through 31 December 2005, 2047 LD patients were notified in the Netherlands. Figure 1 shows the number of notified patients for each year of the study period, with the exception of 188 patients who were part of an outbreak in 1999. [18] In total, 45% of LD patients were most probably infected in the Netherlands, 49% abroad, 5% during hospital admission and of 1% the origin was not known. A sharp rise in number of notified LD patients is seen from 1999 onwards.
Demographic description

For our study population we selected the 928 LD patients who most probably attracted their infection in the Netherlands. For 875 of these, table 1 shows age and gender distribution as well as certainty of diagnosis over the years of the study period. The male to female ratio over the entire period was 2.3 to one. For 53 included patients (5.7%) age and gender data were not complete.

Geographic variation in incidences

For 159 of the 466 municipalities (34%), no LD patients were notified in the 1987–2005 period. The standardised mean municipal LD incidence rate for the remaining 307 municipalities was 0.36 per 100,000 per year (standard deviation: 0.48). The incidence rate ranged from 0.04 to 5.6 per 100,000 per year. Figure 2 shows the geographic variation in the Netherlands using three incidence categories.

Table 1. Age and gender of 875 confirmed and probable Legionnaires’ disease patients in the Netherlands, 1987–2005, excluding travel abroad and nosocomial patients.

<table>
<thead>
<tr>
<th>year</th>
<th>confirmed Legionnaires’ disease patients</th>
<th>probable Legionnaires’ disease patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>men</td>
<td>women</td>
</tr>
<tr>
<td></td>
<td>mean age (range) in years</td>
<td>mean age (range) in years</td>
</tr>
<tr>
<td>1987</td>
<td>4 49 (34–67)</td>
<td>0 n.a.</td>
</tr>
<tr>
<td>1988</td>
<td>7 59 (46–68)</td>
<td>3 45 (38–52)</td>
</tr>
<tr>
<td>1989</td>
<td>7 60 (42–82)</td>
<td>5 40 (24–66)</td>
</tr>
<tr>
<td>1990</td>
<td>13 58 (35–88)</td>
<td>2 62 (47–76)</td>
</tr>
<tr>
<td>1991</td>
<td>2 68 (47–89)</td>
<td>1 49</td>
</tr>
<tr>
<td>1992</td>
<td>2 49 (47–51)</td>
<td>1 35</td>
</tr>
<tr>
<td>1993</td>
<td>9 59 (32–87)</td>
<td>2 43 (29–57)</td>
</tr>
<tr>
<td>1994</td>
<td>9 60 (43–75)</td>
<td>8 45 (30–52)</td>
</tr>
<tr>
<td>1995</td>
<td>8 55 (43–72)</td>
<td>3 49 (29–63)</td>
</tr>
<tr>
<td>1996</td>
<td>4 52 (33–65)</td>
<td>3 55 (30–81)</td>
</tr>
<tr>
<td>1997</td>
<td>4 63 (44–75)</td>
<td>1 43</td>
</tr>
<tr>
<td>1998</td>
<td>13 56 (38–72)</td>
<td>2 48 (47–48)</td>
</tr>
<tr>
<td>1999</td>
<td>21 53 (29–79)</td>
<td>5 54 (43–67)</td>
</tr>
<tr>
<td>2000</td>
<td>30 56 (35–82)</td>
<td>13 50 (27–76)</td>
</tr>
<tr>
<td>2001</td>
<td>28 60 (39–83)</td>
<td>11 58 (48–82)</td>
</tr>
<tr>
<td>2002</td>
<td>79 56 (44–82)</td>
<td>53 54 (21–92)</td>
</tr>
<tr>
<td>2003</td>
<td>66 57 (41–84)</td>
<td>29 57 (5–92)</td>
</tr>
<tr>
<td>2004</td>
<td>85 58 (23–82)</td>
<td>27 64 (21–87)</td>
</tr>
<tr>
<td>2005</td>
<td>100 59 (27–93)</td>
<td>16 59 (18–88)</td>
</tr>
<tr>
<td>total</td>
<td>491 57 (11–95)</td>
<td>185 56 (5–92)</td>
</tr>
</tbody>
</table>
Figure 3. Provincial and national incidence rate of Legionnaires’ disease with origin of infection most probably in the Netherlands, 1987–1998 versus 1999–2005

Diagnostic and inclusion bias

The response for the 1998/99 medical microbiologist questionnaire was 100% and for the 2002/03 questionnaire 82%. The mean number of requested diagnostic LD tests per 100,000 inhabitants of the laboratories’ regions of adherence was 147 (range: 21–465). On average, 2.4% of the requested diagnostic LD tests were positive (range: 0–9%). While the response rate to the second questionnaire was 82%, 353 of 385 (92%) of the notified LD patients of 2000 and 2001 included in our study were reported by the medical laboratories. In addition, they reported 80 non-notified LD patients resulting in an estimate of the overall underreporting rate of 18.5% (80/353 + 80). The mean ratio of notification after the 1999 outbreak to before 1999 was 7.3 (standard deviation: 2.8), ranging from 3.8 to 13. Figure 3 shows the effect of the 1999 outbreak on LD notification at provincial and national level. Comparing the 1987–1998 to the 1999–2005 period, the incidence of notified LD with probable source of infection in the

Table 2. Price of drinking water and mean standardised Legionnaires disease incidence rate with 95% confidence interval for 307 municipalities of the Netherlands divided into four groups, using 1987–2005 notification data.

<table>
<thead>
<tr>
<th>price of drinking water</th>
<th>mean standardised LD incidence rate per 100,000 inhabitants (95% confidence interval)</th>
<th>number of municipalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euro 1.01 – 1.22</td>
<td>0.44 (0.37–0.50)</td>
<td>81</td>
</tr>
<tr>
<td>Euro 1.23 – 1.34</td>
<td>0.52 (0.33 – 0.70)</td>
<td>70</td>
</tr>
<tr>
<td>Euro 1.35 – 1.60</td>
<td>0.67 (0.51 – 0.83)</td>
<td>81</td>
</tr>
<tr>
<td>Euro 1.61 – 1.97</td>
<td>0.49 (0.42 – 0.56)</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>307</td>
</tr>
</tbody>
</table>

* municipalities with a LD incidence of zero were excluded while attributing municipalities with equal price of drinking water to the same group an optimum was reached of groups that are approximately the same size. LD = Legionnaires’ disease
Despite the absence of a straight dose-effect relation, there is a positive linear association (chi-square for trend=5.2; p=0.02).

Apart from a high water price, three factors on diagnostic activity and underreporting were (borderline) significantly associated with a high LD incidence rate in univariate analysis. In a multiple regression model the association between price of water and incidence was corrected for diagnostic and inclusion bias and remained highly significant (OR=5.1; CI: 3.3–8.0; see table 3). For 159 municipalities with no reported LD patients in the 1987–2005 period the incidence was zero, making it impossible to calculate a standardised incidence rate and correct for age, gender, diagnostic and inclusion bias. However, comparing municipalities with high LD incidence to municipalities with no reported LD patients the crude OR for a price of water above Euro 1.45 was 2.5 (CI: 1.5–4.3).

Table 3. Crude and adjusted odds ratios with 95% confidence interval for risk factors associated with high standardised municipal Legionnaires’ disease incidence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate analysis OR (95% CI)</th>
<th>Multivariate analysis OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High versus low price of 1,000 litres water at municipal level</td>
<td>1.9 (1.5–2.6)</td>
<td>5.1 (3.3–8.0)</td>
</tr>
<tr>
<td>High versus low number of requested diagnostic LD tests per 100,000</td>
<td>1.7 (1.2–2.4)</td>
<td>2.1 (1.4–3.3)</td>
</tr>
<tr>
<td>High versus low ratio of positive diagnostic LD tests to requested tests</td>
<td>1.2 (0.9–1.7)</td>
<td>1.8 (1.2–2.8)</td>
</tr>
<tr>
<td>Ratio of notified LD in 1999–2005 period to 1987–1988 period</td>
<td>0.8 (0.6–1.0)</td>
<td>0.8 (0.6–1.0)</td>
</tr>
<tr>
<td>High versus low ratio of underreporting</td>
<td>1.4 (1.0–1.9)</td>
<td>3.1 (2.0–4.9)</td>
</tr>
</tbody>
</table>

* Multiple logistic regression model
b OR (95% CI) = Odds ratio (95% confidence interval)

c LD = Legionnaires’ disease
DISCUSSION

Principle findings

Our results show that a high price for 1,000 litres of water was an independent risk factor for high standardised LD incidence at the municipal level. The association remained highly significant upon correction for differences in diagnostic activity and underreporting.

Strengths and weaknesses of the study

The association between LD incidence and price of water as a proxy for environmental exposure has been corrected for several factors. In general, geographical differences in age and gender standardised LD incidence can be due to differences in environmental exposure, diagnostic activity, underreporting, behavioural differences and differences in the distribution of host susceptibility in the population. The latter two factors were not included in our study and are may therefore limit the generalisability of our conclusions. However, we did include three different measures of diagnostic activity, two of which appeared to be independent factors in the multiple logistic regression model. Furthermore, we showed that underreporting also was an independent factor. We used the price of water in 2004, whereas the price may have developed in an uneven way during the 18.5 years of our study period. However, we know that the changes in the price of water during the 1992–2002 period have been both moderate and general, mostly due to mergers by water companies. [20] If there has been an effect of these mergers, it is likely this diluted any association, implicating that our study underestimated the size of the actual association. The use of price of water as a proxy for the type of raw material used in the production of drinking water in the Netherlands seems justified given the higher operational, depreciation and capital costs for water companies using surface water instead of ground water. [24] Table 2 does not show a straight dose-response relation between higher price and higher incidence, which may be due to merger effects as well (price levelling for adjacent regions of high and low incidence).

Relation to other studies

In the 1990s several studies on geographical differences in LD incidence have been conducted by Bhopal [25,26,27] who points to six sources of bias: [28] data set errors, random fluctuations, variation in time, variation in definition, differences in tests, and diagnostic activity. Our study has taken the latter four sources into account. First, using data from the 1987–2005 period the effect of variation in time has been reduced. Second, our case definition has been applied to all reported LD cases since 1987. The case definition used in our study has been operational in the Netherlands since 2003 and is stricter than notification criteria used in the 1987–2003 period in terms of clinical presentation, radiographic findings and laboratory findings. Third, test variation that is mostly due to serology has not played as dominant a role as in the 1990s after the introduction of the urinary antigen test. In our study population 27% of LD patients was diagnosed by serology. Fourth, as described above we included several measures
of diagnostic activity. With respect to the outcome of our study, Bhopal has emphasised the role of cooling towers as an explanation for geographic differences, whereas our study has focussed on the price of water as a proxy for type of raw material used in water production in a geographical area. Our approach is more general and still leaves room for a possible role of cooling towers or any other aerosol-producing device in the dissemination of *Legionella* bacteria.

**Possible mechanisms and implications**

An association between a high price of water and a high LD incidence is plausible since *Legionella* species are ubiquitous in natural surface water, [15] which in certain parts of the Netherlands is used in the relatively expensive production of drinking water. The alternative raw material is groundwater that is known to be contaminated to a much lesser degree with *L. pneumophila*, [29] other microorganisms and pollutants. Elimination of these requires less elaborate steps in the drinking water production process, which in turn leads to relatively lower prices. [30] If indeed the use of surface water in the production of drinking water leads more often to (undetectable) initial contamination of water systems that in turn leads to higher incidence of LD, improved disinfection could be an intervention worth considering. Given the increased use of surface water as a raw material for drinking water production in the Netherlands (from 33% to 40% between 1992 and 2002) [20] this could have contributed to the observed increased number of notified LD patients in more recent years, and may give rise to a higher incidence in the future.

**Unanswered questions and future research**

Since this is the first report of an association between cost of water as a proxy for water production type and level of LD incidence, our findings need to be confirmed. Furthermore, the differential presence of *Legionella pneumophila* in the specific water distribution systems of the Netherlands needs to be evaluated. Given the high interlaboratory variability in ability to culture *Legionella pneumophila* [31] this should include molecular microbiology techniques. Also, it might be worthwhile to investigate possible contamination of the water distribution system in circumscribed areas of high LD incidence to identify hitherto unidentified sources of infection (see figure 2).

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