14 Shearer RJ, Davies JH, Gelister JS, Dearnaley DP. Hormonal cytoreduction and radiotherapy for carcinoma of the prostate. *Br J Urol* 1992; **69:** 521–24.
15 Pilepich MV, Krall JM, al-Sarraf M, John MJ, Doggett RL, Sause WT. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomised comparative trial of RTOG. *Urology* 1995; **45:** 616–23.
16 Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997; **37:** 247–52.
17 ICRU Report 50. Prescribing, recording and reporting photon beam therapy. Bethesda, MD: International Commission for Radiation Units and Measurements. 1993.
18 Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991; **21:** 935–39.
19 Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics, 1994. *CA Cancer J Clin* 1994; **44:** 7–26.
20 Dearnaley DP, Melia J. Early prostate cancer—to treat or not to treat? *Lancet* 1997; **349:** 892–93.
21 Middleton RG, Thompson IM, Austenfeld MS, et al. Prostate cancer clinical guidelines panel summary report on the management of clinically localized prostate cancer. *J Urol* 1995; **154:** 2144–48.
22 Lu-Yao GL, Greenberg RE. Changes in prostate cancer incidence and treatment in USA. *Lancet* 1994; **343:** 251–54.
23 Sailer SL, Rosenman JG, Symon JR, Cullip TJ, Chaney EL. The tetrad and hexad: maximum beam separation as a starting point for noncoplanar 3-D treatment planning: prostate cancer as a test case. *Int J Radiat Oncol Biol Phys* 1994; **30:** 439–46.
24 Ten Haken RK, Perez-Tamayo C, Tesser RJ, McShan DL, Fraass BA, Lichter AS. Boost treatment of the prostate using shaped, fixed fields. *Int J Radiat Oncol Biol Phys* 1989; **16:** 193–200.
25 Oldham M, Webb S. The optimization and inherent limitations of 3D conformal radiotherapy treatment plans of the prostate. *Br J Radiol* 1995; **68:** 882–93.
26 Neal AJ, Oldham M, Dearnaley DP. Comparison of treatment techniques and conformal radiotherapy of the prostate using dose-volume histograms and normal tissue complication probabilities. *Radiother Oncol* 1995; **37:** 29–34.
27 Burnet NG, Nyman J, Turesson I, Wurm R, Yarnold JR, Peacock JH. Prediction of normal-tissue tolerance to radiotherapy from in-vitro cellular radiation sensitivity. *Lancet* 1992; **339:** 1570–71.
28 LENT SOMA tables. *Radiother Oncol* 1995; **35:** 17–60.
29 Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general medicine. *J Clin Oncol* 1993; **11:** 570–79.
30 Litwin MS, Hays RD, Fink A. Quality of life outcomes in men treated for localized prostate cancer. *JAMA* 1995; **273:** 129–35.
31 Pollack A, Zagars GK, Starkschall G, et al. Conventional vs conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996; **34:** 555–64.
32 Nguyen LN, Pollack A, Zagars GK. Late effects after radiotherapy for prostate cancer in a randomised dose-response study: results of a self-assessment questionnaire. *Urology* 1998; **51:** 991–97.

Effect of monochloramine disinfection of municipal drinking water on risk of nosocomial Legionnaires' disease

Jacob L Kool, Joseph C Carpenter, Barry S Fields

Summary

Background Many *Legionella* infections are acquired through inhalation or aspiration of drinking water. Although about 25% of municipalities in the USA use monochloramine for disinfection of drinking water, the effect of monochloramine on the occurrence of Legionnaires' disease has never been studied.

Methods We used a case-control study to compare disinfection methods for drinking water supplied to 32 hospitals that had had outbreaks of Legionnaires' disease with the disinfection method for water supplied to 48 control-hospitals, with control for selected hospital characteristics and water treatment factors.

Findings Hospitals supplied with drinking water containing free chlorine as a residual disinfectant were more likely to have a reported outbreak of Legionnaires' disease than those that used water with monochloramine as a residual disinfectant (odds ratio 10·2 [95% CI 1·4–460]). This result suggests that 90% of outbreaks associated with drinking water might not have occurred if monochloramine had been used instead of free chlorine for residual disinfection (attributable proportion 0·90 [0·29–1·00]).

Interpretation The protective effect of monochloramine against legionella should be confirmed by other studies. Chloramination of drinking water may be a cost-effective method for control of Legionnaires' disease at the municipal level or in individual hospitals, and widespread implementation could prevent thousands of cases.

Lancet 1999; **353:** 272–77

Respiratory Diseases Branch, Division of Bacterial and Mycotic Diseases (J L Kool MD, B S Fields PhD), **Hospital Infections Program** (J C Carpenter PE)**; and Epidemic Intelligence Service** (J L Kool), **Centers for Disease Control and Prevention, Atlanta, Georgia, USA**

Correspondence to: Dr Jacob Kool, University of Southern California and County of Los Angeles Department of Health Services, 313 North Figueroa Street, Room 212, Los Angeles, CA 90012, USA
(e-mail: jkool@ibm.net)

Introduction

Each year 8000 to 18 000 cases of Legionnaires' disease occur in the USA, 10–20% as part of outbreaks.[1,2] Case-fatality rates in outbreaks typically are 20–40%.[2] The disease is caused by species of the genus *Legionella*, bacteria that live in symbiosis with amoebae in the biofilm that covers the inside of water-containing pipes and tanks. These bacteria thrive in warm (25–42°C) water, particularly in areas where water stagnates. Transmission occurs through inhalation of an aerosol containing the bacteria or by aspiration of contaminated water. Most outbreaks have been traced to either drinking water or cooling towers, and ecological and laboratory studies show that sporadic cases are caused by the same sources.[3–5] Most nosocomial outbreaks have been linked to a hospital drinking water system that had been colonised by *Legionella* spp. Current guidelines from the US Centers for Disease Control and Prevention (CDC) recommend that such hospitals decontaminate the water and then implement control measures aimed at preventing regrowth. These long-term control measures include increasing the temperature of their hot water, continuously injecting additional chlorine, or both.[6] Although these methods are effective, a high water temperature increases the risk of scalding and a continuously high concentration of chlorine can cause corrosion of plumbing systems. Other methods for control of legionella are more expensive and have not been proven more effective than chlorination.

Monochloramine has been used for drinking water disinfection since 1916.[7,8] It is formed when ammonia and free chlorine are mixed in water. Municipal drinking water disinfection has two stages: initial disinfection to kill organisms in the water coming into the treatment plant, and residual disinfection to maintain biocidal activity in the end product throughout the water distribution system. Monochloramine's disinfecting action is slower than that of free chlorine, so it is less useful for initial disinfection. On the other hand it is more stable than free chlorine, so a disinfecting residual can be maintained over long distances in a distribution system, which can reduce cost.[8] Monochloramine penetrates better into biofilm than free chlorine and is more able to kill sessile biofilm bacteria such as some *Pseudomonas* spp.[9–11]

The US Environmental Protection Agency has issued regulations to reduce adverse health effects, including cancer, associated with disinfectants and disinfection by-products (http://www.epa.gov/OGWDW/mdbp/dbp1.html; accessed Dec 4, 1998). Many water treatment plants are considering using monochloramine instead of free chlorine as a residual disinfectant because monochloramine usage minimises the formation of disinfection by-products such as trihalomethanes and haloacetic acids. Consensus is that monochloramine probably poses a lower risk of cancer than free chlorine when used for residual disinfection. A survey in 1989 and 1990 of municipal water utilities in the USA that serve populations greater than 50 000 found that 23% were using monochloramine as residual disinfectant and that others were considering switching to monochloramine.[8] Currently, a typical monochloramine-using water treatment plant uses free chlorine for initial disinfection and monochloramine for residual disinfection.

Little is known about the effect of monochloramine on legionella. In the only study that attempted to measure this effect, monochloramine was added to a model water system containing planktonic (free-floating) *Legionella pneumophila* in previously sterilised water.[12] Monochloramine was more effective than free chlorine. We could find no data about the effect of monochloramine on amoebae.

In investigations in which CDC participated, we noticed that legionella was isolated from many drinking water samples in three municipalities that used free chlorine for residual disinfection but that all samples of drinking water from four municipalities that used monochloramine were free of legionella.[13–17] All samples had been treated with sodium thiosulphate immediately after collection to neutralise the disinfectant. To assess whether municipal water-disinfection practices were associated with risk of legionellosis, we did a case-control study of hospitals.

Methods

Identification of outbreaks and case definition

A case was defined as a hospital in the USA that had experienced at least one outbreak of Legionnaires' disease associated with drinking water that had been reported in a peer-reviewed journal, at a scientific meeting, or as an official CDC report. We did a MEDLINE search to identify all published nosocomial outbreaks of Legionnaires' disease in the USA since 1977. (Search criteria: *Legionella*, *Legionella pneumophila*, legionellae, Legionellaceae, legionellosis, or Legionnaires' disease; and nosocomial, hospital, nosocomial infection, hospital infection, or hospital-acquired.) Whenever an abstract suggested eligibility for inclusion in our study, the article was retrieved. Bibliographies of all retrieved articles were searched for additional pertinent articles or scientific presentations. We also reviewed CDC archives for publications, presentations, and unpublished CDC reports. We selected only those outbreaks in which the drinking water system had been implicated as the source by epidemiological study and confirmed by isolation of identical strains of legionella from patients and drinking water. We excluded outbreaks associated with cooling towers or other aerosol-producing devices not directly associated with drinking water, but we included outbreaks associated with devices that had been contaminated directly from drinking water. Information on location and period of the outbreak was extracted from the publication. Whenever the published information on an outbreak was insufficient for our study, we contacted one of the investigators who reported that outbreak or the relevant hospital infection control staff.

Selection of controls

Controls were defined as hospitals that had not had any reported outbreaks of nosocomial Legionnaires' disease associated with drinking water. We randomly selected hospitals from the American Hospital Association guide to the health care field.[18]

The hospitals that had had outbreaks were predominantly large hospitals of more than 200 beds, but the great majority of the hospitals listed in the American Hospital Association guide have less than 200 beds. Small hospitals are more likely to be located in small cities, which may be less likely to use monochloramine.[8] To avoid selecting too many small hospitals as controls, we category-matched hospitals according to size (more or less than 200 staffed beds). Because a large proportion (72%) of the oubreaks occurred in hospitals with transplant programmes, and because transplantation greatly increases the risk of Legionnaires' disease, we frequency-matched hospitals by whether they had an active transplant programme for tissue or organs. Because the identified outbreaks occurred between 1979 and 1997, each control was randomly assigned a year from 1979 to 1997, and information was collected about water treatment during that year.

Case-control study

We identified the water-treatment plant that supplied water to the hospital. We contacted, within each municipality, a person responsible for drinking-water disinfection; a questionnaire was administered about source and treatment of drinking water supplied to the selected hospital during the period of the outbreak (or, in the case of controls, the randomly assigned year). We asked for the following information: the total population served by the water utility, the average amount of water produced per day, the source of the water (ground or surface), type of initial disinfection, the type and concentration of residual disinfectant, and the pH of the end product.

Data were analysed by means of the Mann-Whitney *U* test for continuous variables and Mantel-Haenszel stratified analysis for binomial variables with the computer program Epi-Info, version 6. We calculated the crude odds ratio for use of chlorine versus use of monochloramine and the adjusted odds ratio with control for hospital size and for the existence of a transplant programme to account for the matched study design. We used maximum likelihood estimation for the odds ratio and exact estimation of the 95% CI. The attributable proportion was estimated by the formula (the adjusted odds ratio replaced the relative risk):

$$\text{Attributable proportion} = \frac{\text{relative risk-1}}{\text{relative risk}}$$

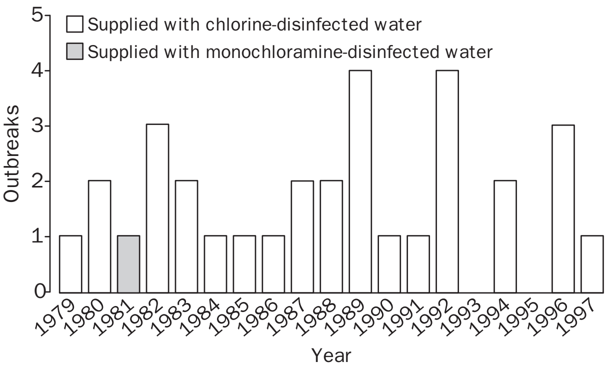

Figure 1: **Nosocomial Legionnaires' disease outbreaks in the USA associated with potable water identified through literature review**

To assess possible interaction and confounding, we did multivariate logistic regression analysis using the GENMOD procedure of SAS, version 6.12. All continuous variables were categorised because none of them satisfied the linearity assumption. Starting with a full model we eliminated factors one by one, depending on their significance as confounders or effect modifiers and on the effect of their elimination on the precision of the odds-ratio estimation for the main exposure variable. Hospital size and the existence of a transplant programme were kept in the model to account for the study design.

Results

We found 31 publications,[13,16,19–47] four presentations,[15,48–50] and one unpublished CDC report (B J Marston, personal communication, May, 1998) describing 32 nosocomial outbreaks of Legionnaires' disease in which drinking water had been implicated as the source by epidemiological study and by laboratory analysis. The outbreaks occurred between 1979 and 1997 (figure 1). The geographical distribution of the outbreaks is shown in figure 2. 27 outbreaks were apparently associated with inhalation of contaminated aerosol from showers or taps, or with aspiration of the water; three were traced to cleaning of respiratory devices with tap-water; one was associated with consumption of contaminated ice made from tap-water; and one was associated either with a cooling tower directly contaminated with drinking water or with drinking-water aerosols. One outbreak involved surgical-wound infections with legionella as well as cases of Legionnaires' disease.

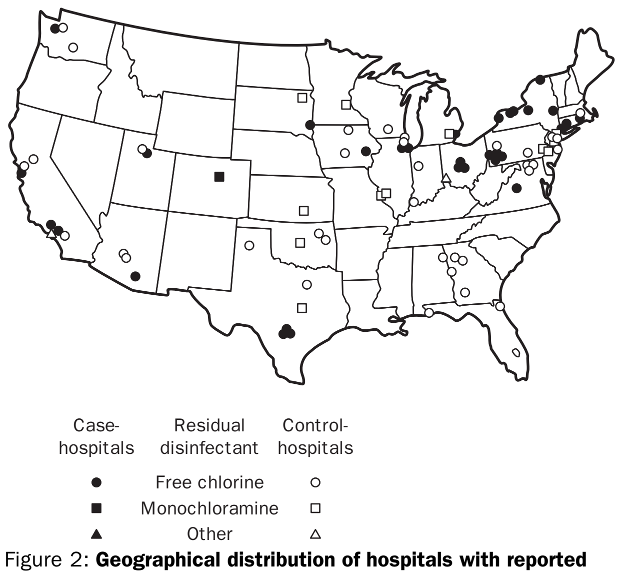

Figure 2: **Geographical distribution of hospitals with reported Legionnaires' disease outbreaks associated with potable water and of randomly selected control-hospitals**

Some overlapping points dispersd to improve legibility. One free-chlorine control-hospital in Hawaii not shown.

None of the municipalities had changed the water disinfection process during the period of the outbreak. 31 outbreaks occurred in hospitals supplied with water containing only free chlorine for residual disinfection. The only other outbreak happened in 1981 in Denver, which had used monochloramine for both initial and residual disinfection since 1917.[7] This outbreak involved three patients in 1981; one additional patient was identified in 1983.[24] The main intervention was removal of large water tanks in which warm water stagnated for periods of up to 1 week, and installation of instantaneous water heaters.

Case-control study results

We randomly selected 50 control-hospitals. One control-hospital was supplied with drinking water that was disinfected alternately with chlorine and monochloramine, another was supplied with water disinfected with chlorine dioxide. These two hospitals were excluded from the statsitical analysis. Private wells supplied one case-hospital and one-control hospital; hospital staff provided information on these water supplies. The geographical distribution of cases and controls is shown in figure 2. Water supplied to case-hospitals and control-hospitals was similar in respect to water source, size of population supplied by the water plant, pH, and all other water treatment variables (table).

Case-hospitals were more likely than control-hospitals to be supplied with water containing free chlorine as a residual disinfectant (crude odds ratio 10·1 [95% CI 1·4–456]; adjusted odds ratio 10·2 [1·4–460]).

In the logistic-regression analysis the following factors did not contribute significantly to the model and were eliminated: time of outbreak (or randomly assigned year for controls), population supplied by the water plant, amount of water produced by the plant, type of initial disinfection, type of source water (surface or ground), concentration of the residual disinfectant, the interaction term of type of residual disinfectant and concentration, pH of the end product, and the interaction term of pH and type of residual disinfectant. The only variable that was significant was type of residual disinfectant. Although neither hospital size nor existence of a transplant programme contributed significantly, these factors were kept in the model to account for the matched study design. Using this logistic-regression model, we found an adjusted odds ratio of 10·8 (1·9–203) for use of free chlorine versus monochloramine as residual disinfectant.

Because in the stratified analysis some cell values were small or zero, we took as the best estimation the adjusted odds ratio derived with the maximum likelihood estimation and exact confidence interval. The attributable proportion estimated from this odds ratio was 0·90 (0·29–1·00), suggesting that about 90% of nosocomial outbreaks of Legionnaires' disease associated with drinking water could be prevented if every municipality used monochloramine as a residual disinfectant.

Discussion

Our results show that use of monochloramine for residual disinfection of drinking water was associated with a lower

Characteristic	Case-hospitals (n=32)	Control-hospitals (n=48)*	Adjusted odds ratio (95% CI)	p
Characteristics of hospitals				
Number of distinct municipal water distribution systems	26	45		
200 beds or more	31	46		
Transplant programme	23 (72%)	35 (73%)		
Median (range) year of outbreak	1988·5 (1979–97)	1988 (1979–97)		0·89†
Residual disinfectant				
Free chlorine	31	36	10·2 (1·4–460)	0·007
Monochloramine	1	12‡	1·0§	
Initial disinfectant				
Free chlorine	31	43	2·1 (0·16–114)	0·46
Monochloramine	1	3	1·0§	
Alternating chlorine/monochloramine	0	1	Excluded	
Ozone	0	1	Excluded	
Water source				
Surface	22	33		0·91†‖
Ground	5	10		
Mix of surface/ground	5	5		
Median (range) number of people supplied by water utility	242 500 (5000–4 000 000)	198 000 (3500–9 000 000)		0·28†
Median (range) pH of finished water	7·6 (7·0–10·0)	7·8 (7·0–10·5)		0·82†

*Not including one hospital supplied with water containing chlorine dioxide, and one hospital supplied with chlorinated water as well as chloraminated water, from separate water-treatment plants that supplied one water-distribution system. †Mann-Whitney *U* test; ‡Including one hospital supplied with water that contained free chlorine for 2 weeks per year. §Reference category. ‖Proportion surface water analysed as a continuous variable.

Characteristics of case-hospitals and control-hospitals and their municipal water suppliers

likelihood of outbreaks of Legionnaires' disease. More precisely, we found that hospitals supplied with water containing only free chlorine were 10·2 times more likely to experience an outbreak associated with drinking water that was subsequently investigated and reported in a peer-reviewed journal, at a scientific meeting, or as a CDC report.

Our finding is supported by laboratory tests finding that legionella were frequently recovered from chlorinated municipal water[13,15,16] but not from chloraminated water[14,15,17] in recent CDC-assisted investigations. Monochloramine diffuses better than chlorine does into stagnant water because of its slower decay, and it penetrates better into biofilm.[9–11] It may be more effective, therefore, in the biological niche of legionella, and it is known to be effective against planktonic legionella.[12] Activity of monochloramine against amoebae appears not to have been studied yet but may be important.

Study limitations

Hospitals were classified as cases or controls depending on whether outbreaks had been detected, investigated, and reported. Some of the control municipalities may have experienced legionellosis outbreaks that were never detected or reported, resulting in misclassification. For any given outbreak, however, a reasonable assumption is that the likelihood of a hospital detecting and reporting this outbreak is independent of the method of disinfection because we do not think that an association between municipal disinfection and risk of Legionnaires' disease has been made previously. Therefore, non-detection and non-publication of outbreaks leads to non-differential misclassification and can introduce a bias only towards the null. In other words, it will lead to underestimation of the protective effect of monochloramine. The same is true for misclassification of case-hospitals due to incorrect identification of drinking water as the source of transmission. Similarly, individual hospital characteristics associated with the risk of contamination of hospital water systems, such as temperature setting of the hospital water heaters and additional water treatment by the hospital (such as copper-silver systems), are all independent of the choice of disinfectant by the municipal water authority and will result in a bias towards the null. We preferred to work with this non-differential misclassification rather than undertake interviews of each hospital, because that would have introduced a reporting bias.

A potential confounder could be the association between the size of the municipal water system and the size and number of hospitals it serves. The need to maintain adequate concentrations of residual disinfectant over longer distances can be a reason for water-treatment plants covering large areas to choose monochloramine. Risk factors for nosocomial outbreaks include hospital size[15,51] and the presence of immunocompromised patients, especially transplant recipients.[2,15] Large tertiary-care hospitals are also more likely to be affiliated to universities and so to have staff interested in publishing in peer-reviewed journals. However, as a result of the matched design of the study, case-hospitals and control-hospitals were similar in regard to hospital size and the existence of a transplant programme, and municipal water-treatment plants supplying case-hospitals were of similar size to those supplying controls (table).

The proportion of municipalities using monochloramine varies by geographical location and may be highest in southeast USA,[8] although none of our control-hospitals there were supplied with chloraminated water (figure 2). In addition, there are regional differences in the incidence of outbreaks of Legionnaires' disease, with the lowest incidence in the Southeast.[2] We were concerned that matching by geographical area could have resulted in overmatching because the geographical variation in disease incidence might actually have been caused by regional differences in the method of drinking-water disinfection. Exclusion of the southeast from our analysis would evidently have resulted in a higher odds ratio estimate. In addition, regulation of water temperature in hospitals to avoid scalding injuries, by state health departments, is probably not correlated with choice of disinfectant for drinking water by municipal water authorities and therefore should not have been a confounder in this study.

Implications

Monochloramine for disinfection can be inexpensive; it involves installation of automated injection devices for ammonia and chlorine, and training of staff. A 1990 survey of four municipalities found that switching from free chlorine to monochloramine cost from at least $5000 to as much as $185 000. The highest of these costs was incurred because that facility's building had to be expanded to house the additional equipment. Ammonia was purchased at a cost of $0.75 to $6.16 per million gallons of water treated.[8]

Chloramination of individual hospital water systems for control of nosocomial legionellosis is an option that deserves further evaluation. A chloramination booster station could be installed in a chlorine-using water system to chloraminate only a small part of that system, such as a hospital campus. This method may be better than other options: it will cause less corrosion than continuous supplemental chlorination,[8] it will not increase risk of scalding, and it may be simpler, more effective, and cheaper than other long-term disinfection methods.

Our finding of a protective effect of monochloramine on Legionnaires' disease associated with drinking water will need to be confirmed by other studies. The decision by municipal water authorities to switch to monochloramine depends on many complex factors; prevention of Legionnaires' disease may become an additional argument in favour of this switch. Most cases of Legionnaires' disease are community-acquired and sporadic, but, like outbreaks, many sporadic cases have been traced to potable water. An estimated 8000–18 000 cases of Legionnaires' disease occur in the USA each year.[1] If at least half of all legionella infections were acquired from drinking water, 90% of these, or 3600–8100 cases, would be prevented each year in the USA if all municipalities used monochloramine. If overall mortality is 25%,[2] this would result in prevention of 900–2025 deaths per year.

Contributors

Jacob Kool noticed the lower rate of legionellosis outbreaks in municipalities that use monochloramine, designed the study, collected data, did the analysis, and wrote the paper. Joseph Carpenter designed the study, collected data, contributed to the analysis, and critically reviewed the paper. Barry Fields contributed to study design and analysis, and critically reviewed the paper.

Acknowledgments

We thank Sharon Kool-Hiemcke for general support, David G Kleinbaum, Emory University School of Public Health, and Brian Plikaytis, CDC, for reviewing the statistical analysis; Jay C Butler, Robert F Breiman, Cynthia G Whitney, and Anne Schuchat, CDC, for critically reviewing the paper.

References

1 Marston BJ, Plouffe JF, File TM, et al. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active suveillance study in Ohio. *Arch Intern Med* 1997; **157:** 1709–18.

2 Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease: risk factors for morbidity and mortality. *Arch Intern Med* 1994; **154:** 2417–22.

3 Bhopal RS, Fallon RF, Buist EC, Black RJ, Urquhart JD. Proximity of the home to a cooling tower and risk of non-outbreak Legionnaires' disease. *BMJ* 1991; **302:** 378–83.

4 Stout JE, Yu VL, Muraca P, Joly J, Troup N, Tompkins LS. Potable water as a cause of sporadic cases of community-acquired Legionnaires' disease. *N Engl J Med* 1992; **326:** 151–55.

5 Straus WL, Plouffe JF, File TM Jr, et al. Risk factors for domestic acquisition of Legionnaires' disease. *Arch Intern Med* 1996; **156:** 1685–92.

6 Centers for Disease Control and Prevention. Guidelines for prevention of nosocomial pneumonia. *MMWR Morb Mortal Wkly Rep* 1997; **46:** 1–79.

7 Dice J. Denver's seven decades of experience with chloramination. *J Am Water Works Assoc* 1985; **77:** 34–37.

8 Kirmeyer GJ, Foust GW, Pierson GL, Simmler JJ, LeChevalier MW. Optimizing chloramine treatment. Denver: American Water Works Research Foundation, 1993.

9 LeChevalier MW, Cawthon CD, Lee RG. Inactivation of biofilm bacteria. *Appl Environ Microbiol* 1988; **54:** 2492–99.

10 Chen X, Stewart PS. Chlorine penetration into artificial biofilm is limited by a reaction-diffusion interaction. *Environ Sci Technol* 1996; **30:** 2078–83.

11 Samrakandi MM, Roques C, Michel G. Influence of trophic conditions on exopolysaccharide production: bacterial biofilm susceptibility to chlorine and monochloramine. *Can J Microbiol* 1997; **43:** 751–58.

12 Cunliffe DA. Inactivation of *Legionella pneumophila* by monochloramine. *J Appl Bacteriol* 1990; **68:** 453–59.

13 Centers for Disease Control and Prevention. Sustained transmission of nosocomial Legionnaires' disease—Arizona and Ohio. *MMWR Morb Mortal Wkly Rep* 1997; **46:** 416–21.

14 Kool JL, Warwick MC, Pruckler JM, Brown EW, Butler JC. Outbreak of Legionnaires' disease at a bar after basement flooding. *Lancet* 1998; **351:** 1030.

15 Kool JL, Bergmire-Sweat D, Brown EW, et al. The tepid zone: risk factors for nosocomial transmission of Legionnaires' disease and for colonization of hospital water systems by *Legionella*. In: the eighth annual meeting of the Society for Healthcare Epidemiology of America, Orlando. Mt Royal, New Jersey: Society for Healthcare Epidemiology of America, 1998: 39.

16 Kool JL, Fiore AE, Kioski CM, et al. More than ten years of unrecognized nosocomial transmission of Legionnaires' disease among transplant patients. *Infect Control Hosp Epidemiol* 1998; **19:** 898–904.

17 Buchholz U, Peterson C, Kool J, et al. 1-800-DNA-TYPE: strengths and limitations of molecular subtyping in a community outbreak of Legionnaires' disease in Los Angeles County. In: 38th Interscience Conference on Antimocrobial Agents and Chemotherapy, San Diego. Washington: American Society for Microbiology, 1998: 583.

18 American Hospital Association. The AHA guide to the health care field. Chicago: American Hospital Association, 1993.

19 Arnow PM, Chou T, Weil D, Shapiro EN, Kretzschmar C. Nosocomial Legionnaires' disease caused by aerosolized tap water from respiratory devices. *J Infect Dis* 1982 **146:** 460–67.

20 Best M, Yu VL, Stout J, Goetz A, Muder RR, Taylor F. Legionellaceae in the hospital water-supply: epidemiological link with disease and evaluation of a method for control of nosocomial Legionnaires' disease and Pittsburgh pneumonia. *Lancet* 1983; ii: 307–10.

21 Blatt SP, Parkinson MD, Pace E, et al. Nosocomial Legionnaires' disease: aspiration as a primary mode of disease acquisition. *Am J Med* 1993; **95:** 16–22.

22 Brady MT. Nosocomial Legionnaires' disease in a children's hospital. *J Pediatr* 1989; **115:** 46–50.

23 Breiman RF, Fields BS, Sanden GN, Volmer L, Meier A, Spika JS. Association of shower use with Legionnaires' disease: possible role of amoebae. *JAMA* 1990; **263:** 2924–26.

24 Brown A, Lema M, Ciesielski CA, Blaser MJ. Combined plasmid and peptide analysis of clinical and environmental *Legionella pneumophila* strains associated with a small cluster of Legionnaires' disease cases. *Infection* 1985; **13:** 163–66.

25 Ciesielski CA, Blaser MJ, Wang WL. Role of stagnation and obstruction of water flow in isolation of *Legionella pneumophila* from hospital plumbing. *Appl Environ Microbiol* 1984; **48:** 984–87.

26 Cordes LG, Wiesenthal AM, Gorman GW, et al. Isolation of *Legionella pneumophila* from hospital shower heads. *Ann Intern Med* 1981; **94:** 195–97.

27 Doebbeling BN, Ishak MA, Wade BH, et al. Nosocomial *Legionella micdadei* pneumonia: 10 years experience and a case-control study. *J Hosp Infect* 1989; **13:** 289–98.

28 Graman PS, Quinlan GA, Rank JA. Nosocomial legionellosis traced to a contaminate ice machine. *Infect Control Hosp Epidemiol* 1997; **18:** 637–40.

29 Green M, Wald ER, Dashefsky B, Barbadora K, Wadowsky RM. Field inversion gel electrophoretic analysis of *Legionella pneumophila* strains associated with nosocomial legionellosis in children. *J Clin Microbiol* 1996; **34:** 175–76.

30 Hanrahan JP, Morse DL, Scharf VB, et al. A community hospital outbreak of legionellosis; transmission by potable hot water. *Am J Epidemiol* 1987; **125:** 639–49.

31 Heimberger T, Birkhead G, Bornstein D, Same K, Morse D. Control of nosocomial Legionnaires' disease through hot water flushing and supplemental chlorination of potable water. *J Infect Dis* 1991; **163:** 413.

32 Helms CM, Massanari RM, Wenzel RP, Pfaller MA, Moyer NP, Hall N. Legionnaires' disease associated with a hospital water system:

a five-year progress report on continuous hyperchlorination. *JAMA* 1988; **259:** 2423–27.

33 Johnston JM, Lathan RH, Meier FA, et al. Nosocomial outbreak of Legionnaires' disease: molecular epidemiology and disease control measures. *Infect Control* 1987; **8:** 53–58.

34 Johnson JT, Yu VL, Best MG, et al. Nosocomial legionellosis in surgical patients with head-and-neck cancer: implications for epidemiological reservoir and mode of transmission. *Lancet* 1985; ii: 298–300.

35 Lowry PW, Blankenship RJ, Gridley W, Troup NJ, Tompkins LS. A cluster of *Legionella* sternal-wound infections due to postoperative topical exposure to contaminated tap water. *N Engl J Med* 1991; **324:** 109–13.

36 Mastro TD, Fields BS, Breiman RF, Campbell J, Plikaytis BD, Spika JS. Nosocomial Legionnaires' disease and use of medication nebulizers. *J Infect Dis* 1991; **163:** 667–71.

37 Matulonis U, Rosenfeld CS, Shadduck RK. Prevention of *Legionella* infections in a bone marrow transplant unit: multifaceted approach to decontamination of a water system. *Infect Control Hosp Epidemiol* 1993; **14:** 571–75.

38 Mermel LA, Josephson SL, Giorgio CH, Dempsey J, Parenteau S. Association of Legionnaires' disease with construction: contamination of potable water? *Infect Control Hosp Epidemiol* 1995; **16:** 76–81.

39 Nafziger DA. Successful chlorination for *Legionella* at Henry Ford Hospital. *Infect Dis Clin Pract* 1997; **7:** 118.

40 Nolte FS, Conlin CA, Roisin AJ, Redmond SR. Plasmids as epidemiological markers in nosocomial Legionnaires' disease. *J Infect Dis* 1984; **149:** 251–56.

41 Parry MF, Stampleman L, Hutchinson JH, Folta D, Steinberg MG, Krasnogor LJ. Waterborne *Legionella bozemanii* and nosocomial pneumonia in immunosuppressed patients. *Ann Intern Med* 1985; **103:** 205–10.

42 Plouffe JF, Para MF, Maher WE, Hackman B, Webster L. Subtypes of *Legionella pneumophila* serogroup 1 associated with different attack rates. *Lancet* 1983; ii: 649–50.

43 Plouffe JF, Webster LR, Hackman B. Relationship between colonization of hospital building with *Legionella pneumophila* and hot water temperatures. *Appl Environ Microbiol* 1983; **46:** 769–70.

44 Schoonmaker D, Heimberger T, Birkhead G. Comparison of ribotyping and restriction enzyme analysis using pulsed-field gel electrophoresis for distinguishing *Legionella pneumophila* isolates obtained during a nosocomial outbreak. *J Clin Microbiol* 1992; **30:** 1491–98.

45 Shands KN, Ho JL, Meyer RD, et al. Potable water as a source of Legionnaires' disease. *JAMA* 1985; **253:** 1412–16.

46 Snyder MB, Siwicki M, Wireman J, et al. Reduction in *Legionella pneumophila* through heat flushing followed by continuous supplemental chlorination of hospital hot water. *J Infect Dis* 1990; **162:** 127–32.

47 Venezia RA, Agresta MD, Hanley EM, Urquhart K, Schoonmaker D. Nosocomial legionellosis associated with aspiration of nasogastric feedings diluted in tap water. *Infect Control Hosp Epidemiol* 1994; **15:** 529–33.

48 Hanrahan JP, Morse DL, Scharf VB, et al. Community hospital legionellosis outbreak linked to hot-water showers. In: Thornsberry C, Balows A, Feeley JC, eds. *Legionella*: proceedings of the 2nd international symposium. Washington DC: American Society for Microbiology, 1984: 224–25.

49 Lepine L, Jernigan DB, Wyatt B, et al. Use of urinary antigen testing to detect an outbreak of nosocomial Legionnaires' disease. In: abstracts of the 35th interscience conference on antimicrobial agents and chemotherapy. Washington DC: American Society for Microbiology, 1995: 267.

50 Sellick JA, Mylotte JM. Nosocomial *Legionella pneumophila* pneumonia in a hospital with an instantaneous hot water heater. In: Barbaree JM, Breiman RF, Dufour AP, eds. *Legionella*: current status and emerging perspectives. Washington, DC: American Society for Microbiology, 1993: 43–45.

51 Alary M, Joly JR. Factors contributing to the contamination of hospital water distribution systems by legionellae. *J Infect Dis* 1992; **165:** 565–69.