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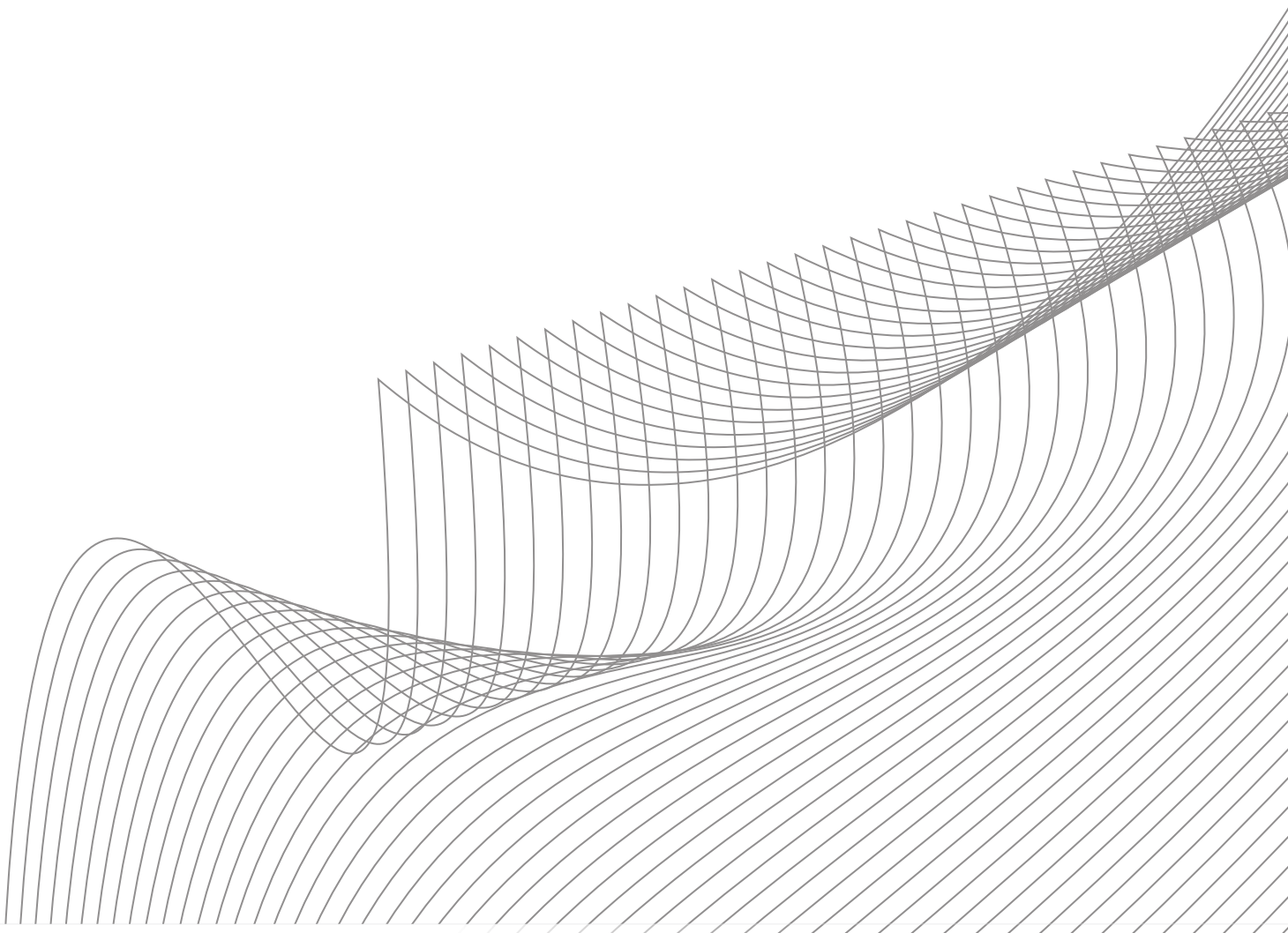
Claire Waller, Kevin Freeman, Shereen Labib, Rob Baird



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Original article

Epidemiological and clinical characteristics of legionellosis in Northern Australia, 2010–2021

Claire Waller, Kevin Freeman, Shereen Labib, Rob Baird

Abstract

Objective

This study describes characteristics of the legionellosis cases occurring between 2010 and 2021 in the Northern Territory (NT), Australia.

Methods

We retrospectively reviewed 53 cases of legionellosis during the defined period and documented patient and clinical characteristics, diagnostics, and seasonality of infection.

Results

All cases were sporadic. The incidence rate in the NT was higher than the Australian median rate (2.1 and 1.5 per 100,000 population per year respectively). Aboriginal and Torres Strait Islander patients presented at a younger age than did non-Indigenous patients (median 41 and 60 years of age respectively), and overall there was a male preponderance. There was a higher proportion of legionellosis in the months with increased humidity, with a greater number of *L. longbeachae* infections detected overall (59%) than of *L. pneumophila* (41%). The majority of cases were diagnosed serologically (57% of *L. pneumophilia* and 93% of *L. longbeachae*).

Conclusions

Legionellosis in the NT is more common, seasonal, and may be underreported due to current reliance on serological testing for diagnosis. The higher incidence of legionellosis, and the younger age of Aboriginal and Torres Strait Islander patients of the NT, have public health implications, given that the clinical presentation of legionellosis is indistinguishable from other forms of pneumonia.

Keywords: Legionella, legionellosis, Northern Territory

Introduction

Legionella bacteria are a group of gram-negative aerobic bacteria which are widespread in the environment.[1] Although more than 90 different species of *Legionella* have been reported, the most common pathogenic species in Australia are *Legionella pneumophila* and *L. longbeachae* which together account for 99% of notified cases.[2,3] *Legionella* spp. are known as opportunistic pathogens which can cause an acute pneumonic illness in susceptible hosts (Legionnaire's disease) that cannot be distinguished clinically from other forms of pneumonia.[1] Infection can also cause a milder, flu-like illness known as Pontiac fever.[1] Although legionellosis can occur in previously healthy individuals, host risk factors are those

which reduce local or systemic cellular immunity or which increase the chances of exposure to the bacteria.[1] Specific risk factors include male gender; cigarette smoking; chronic heart or pulmonary disease; diabetes; end stage renal failure; age greater than 50 years; and immunosuppression.[4]

In the environment, *Legionella* spp. can be found associated with natural aqueous environments and soil, and have also been isolated from man-made systems such as hot and warm water systems; evaporative cooling towers; respiratory therapy devices; shower heads; and potting mixes.[1,5] *Legionella* spp. are acquired via airborne transmission, involving inhalation of *Legionella*-containing aerosols and dust or micro aspiration of contaminated water.[1,4]

Legionellosis is notifiable in Australia and occurs both sporadically and in clusters or outbreaks. In a prospective, multicentre study of community-acquired pneumonia across Australia, *Legionella* spp. were identified as the causative pathogen in 3.4% of cases; however, this was based predominantly in temperate and urban regions of Australia.[6] Underreporting of legionellosis is also common because many sporadic cases are treated empirically without diagnostic testing being performed.

The objective of surveillance for legionellosis in Australia is to identify common sources of infection, especially in relation to clusters and outbreaks, to enable environmental investigation and instigation of control measures. Surveillance is also important to monitor the epidemiology of legionellosis in order to inform better preventative measures.

This report describes the profile, from January 2010 to April 2021, of legionellosis cases in the Northern Territory (NT), encompassing a diverse tropical and arid geographical region comprising rural and remote areas. In addition, Aboriginal and Torres Strait Islander people comprise one quarter of the population (25.5%).[7]

Methods

Patients with legionellosis in the NT, from January 2010 to April 2021, were identified retrospectively, based on the NT Centre for Disease Control (CDC) National Notifiable Disease Database (NNDS) and through laboratory records. These patients were then cross-checked using the centralised laboratory Labtrak database (Intersystems, Cambridge), in addition to results being verified from the state referral laboratory, Westerns (Perth WA). Four additional cases that were not notified were identified through cross-checking with laboratory data.

Testing for legionellosis in the NT is routinely performed on all respiratory presentations to the intensive care unit (ICU), but is not always performed on respiratory presentations to the general wards unless requested by the treating clinician. The specific testing performed is at the discretion of the treating clinician. This usually includes urinary antigen and serology for ward-based respiratory inpatients, in addition to respiratory nasopharyngeal polymerase chain reaction (PCR) testing in ICU or high-risk inpatients.

Cases for inclusion were based on the Australian Government Department of Health legionellosis case definition, with both confirmed and probable cases notified in the NT and investigated.[8] A confirmed case of legionellosis had the following: laboratory definitive evidence AND clinical evidence, comprising 1) isolation of *Legionella* OR detection of *Legionella* urinary antigen OR seroconversion OR significant increase in antibody level OR a fourfold or greater rise to *Legionella*, AND 2) fever OR cough OR pneumonia. A probable case had the following: suggestive laboratory criteria AND clinical evidence, comprising 1) single high titre to *Legionella* OR detection of *Legionella* by nucleic acid testing (NAAT) OR detection of *Legionella* by direct fluorescence assay AND 2) fever AND cough OR pneumonia.

As per the Communicable Diseases Network Australia (CDNA) Legionellosis National Guidelines for Public Health Units, a cluster was defined as two or more cases, linked by area or residence or work, which have sufficient proximity in dates of onset of illness to warrant further investigation.[9] An outbreak was defined as two or more cases where the onset of illness is closely linked in time and where there is epidemiological evidence of a common source of infection.[9]

Serology was tested using an immunofluorescent assay (IFA); a four-fold rise in antibody titre after three to six weeks is predictive of legionellosis.[10] *L. pneumophila* serogroup 1 urinary antigen testing was performed through BinaxNOW™ *in vitro* rapid immunochromatographic assay. The peak of urinary antigen detection for *L. pneumophila* is found at 5–10 days after onset of symptoms.[10] Respiratory *Legionella* NAAT was performed by standard methods at accredited reference laboratories and included PCR for *L. pneumophila* and *L. longbeachae* but not pan-*Legionella* PCR. Culture was not performed.

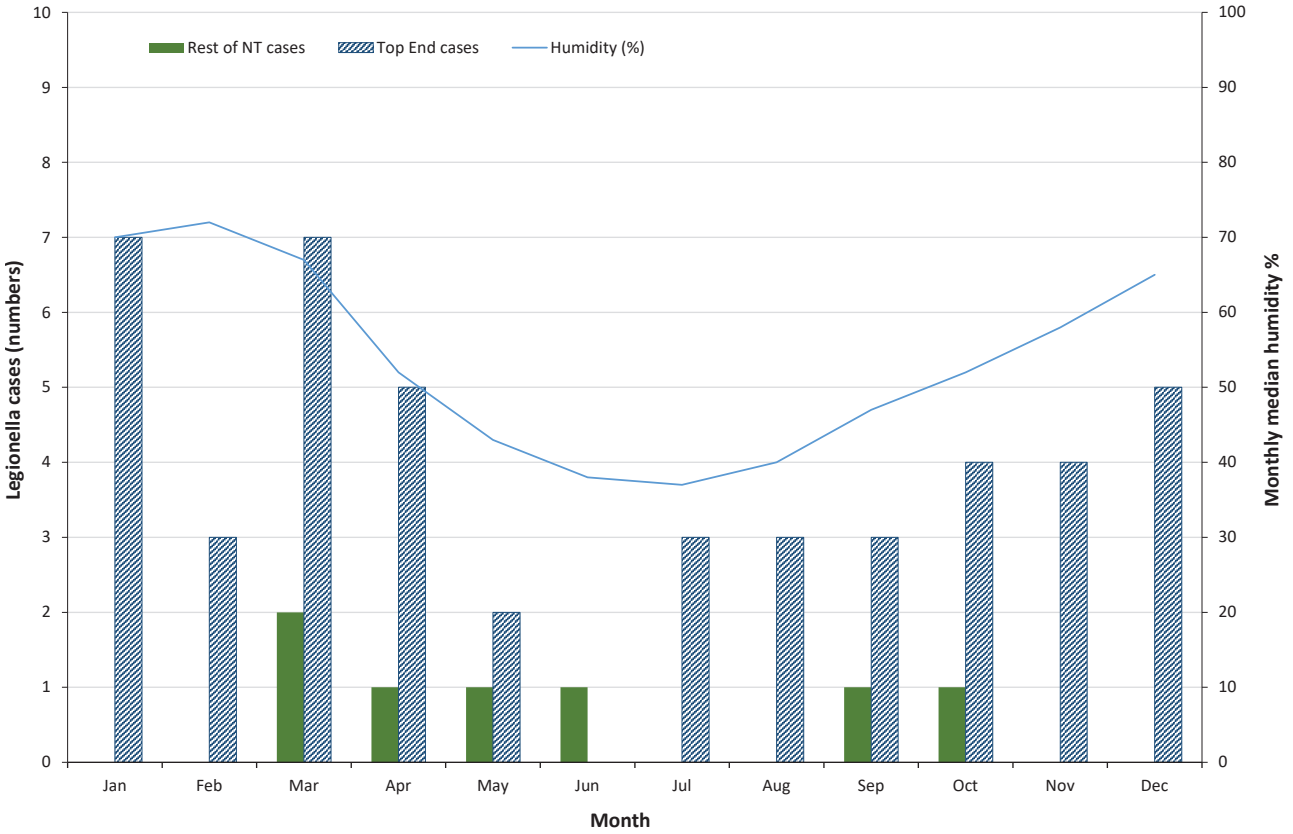
The NT comprises two distinct geographical zones. The Top End of the Northern Territory (TENT) encompasses the northernmost section of Australia covering an area in excess of 500,000 km^2 with a sparse population of 180,000 and a distinct tropical monsoonal season. The TENT includes the regions of Darwin urban, Litchfield, Daly-Tiwi-West Arnhem, East Arnhem and Katherine. The rest of the NT is arid and sparsely populated and encompasses 700,000 km^2 and includes all other regions outside the TENT. The annualised disease incidence was calculated using the NT population data from the 2016 Australian Bureau of Statistics Census which included a population of 228,833 people, of whom one quarter (25.5%) identified as Aboriginal and/or Torres Strait Islander people (58,248 people).[7] The median age of the NT population is 32 years, which is younger than the median age for the rest of Australia (38 years).[7] Areas outside the urban centres of Greater Darwin (Darwin city, Darwin suburbs and Palmerston) were considered rural and remote, with approximately 40% of the NT population residing in rural or remote areas.[7] Incidence rate calculation and descriptive analysis were performed using Microsoft Excel. Categorical variables were analysed with the two-tailed Fisher's exact test using SPSS (IBM *SPSS Statistics for Windows*, version 25.0). The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (Human Research Ethics Committee 2021-3998).

Results

Over the 11-year study period there were 53 patients with legionellosis; two of these cases could not be speciated. All of the cases in the NT were sporadic; there were no clusters or outbreaks. Eighteen of these were confirmed cases and 35 were probable cases based on the Australian Government Department of Health legionellosis case definition. The overall annual infection incidence was 2.1 per 100,000 population per year. The incidence rate was higher among Aboriginal and Torres Strait Islander people (2.5 per 100,000 population per year) than among non-Indigenous people (2.0 per 100,000 population per year). There was overall a higher number of legionellosis cases (38/46, 83%) in the months associated with increased humidity in the TENT, which includes the wet season 'build-up' (September–December: 16/46, 35%) and monsoon (January–April: 22/46, 48%) (Figure 1).

All of the patients had a clinical presentation of pneumonia; there were no patients with Pontiac fever. Of the 53 cases, the median age was 54 years (interquartile range, IQR: 41–67), with a younger cohort found in Aboriginal and Torres Strait Islander patients (median age 41 years) than among non-Indigenous patients (median age 60 years), $p < 0.01$ (Table 1). There was a male preponderance (37/53, 70%). There was no significant difference in incidence rate between urban or rural and remote residence, when accounting for the NT population geographic distribution.

Figure 1: NT *Legionella* cases and humidity by month, January 2010 to April 2021



Of the 51 cases that could be identified by species, there was a higher proportion of *L. longbeachae* 30/51; 59%) than of *L. pneumophila* (21/51; 41 %) (p = 0.21). These epidemiological data are presented in Table 2. Cases due to *L. longbeachae* were identified more frequently in the wet season 'build-up' (14/30; 47%) than were cases due to *L. pneumophila* (4/21; 19%) (p = 0.073); similar numbers of each species were detected in the monsoonal and dry seasons. Patients with *L. longbeachae* infection had documented underlying lung disease more commonly (15/27; 56%) than did those with *L. pneumophila* (4/20; 20%). Smoking status was recorded for 13/21 (62%) *L. pneumophila* and 17/30 (57%) *L. longbeachae* cases, with 10/13 (77%) *L. pneumophila* and 11/17 (65%) *L. longbeachae* patients active or ex-smokers. Similar rates of other comorbidities between the two groups were observed (Table 3), with 15/20 (75%) *L. pneumophila* and 22/27 (81%) *L. longbeachae* cases identified as having concurrent chronic medical conditions. The majority of patients in this study were hospitalised (42/45; 93%), with similar rates of hospitalisation between the two group based on species: 18/20 (90%) of *L. pneumophila* cases and 24/25 (96%) of *L. longbeachae* cases. A greater proportion of patients in the *L. longbeachae* group (9/25; 36%) required admission to ICU than did those in the *L. pneumophila* group (4/20; 20%) (p = 0.327).

Diagnostics

Overall, of the probable cases, 3/35 (9%) were determined as probable based on detection through NAAT alone and 32/35 (91%) (p = 0.55) were classified based on a single high antibody titre. Fifty-seven percent of *L. pneumophila* patients (12/21) and 93% of *L. longbeachae* patients (28/30) were diagnosed serologically. Of the patients who underwent serological testing, the majority were diagnosed based on acute serology, with 10/12 *L. pneumophila* patients (83%) and 19/28 *L. longbeachae* patients (68%) having positive acute serology. Serological titres ranged from 1:64 to 1:>16384 for *L. pneumophilia* and from 1:64 to 1:2048 for *L. longbeachae*. NAAT was more frequently positive in patients with *L. pneumophilia* (4/5; 80%) than those

Table 1: Demographics of patients with *Legionella* infection in the NT from January 2010 to April 2021

Parameter	Aboriginal and/or Torres Strait Islander (% of total)	Non-Indigenous (% of total)	Total (%)	*p* value
Number	**16 (30)**	**37 (70)**	**53 (100)**	
Median age in years (IQR)	41 (39–54)	60 (50–70)	54 (41–67)	0.01
Sex				
Male	10 (63)	27 (73)	37 (70)	
Female	6 (37)	10 (27)	16 (30)	
Residence				
Urban	7 (44)	30 (81)	37 (70)	
Rural and remote	9 (56)	7 (19)	16 (30)	
Comorbidities[a]				
Lung disease	7 (44)	11 (34)	18 (38)	
Other health conditions	10 (63)	25 (78)	35 (73)	
Seasonality of infection[b]				
Monsoon	7 (44)	18 (49)	25 (47)	
Dry	3 (19)	7 (19)	10 (19)	
Wet season 'build-up'	6 (38)	12 (32)	18 (34)	

a Comorbidities were recorded for 16/16 Aboriginal and/or Torres Strait Islander patients and 32/37 non-Indigenous patients.

b In the Top End, the monsoon season spans the months January, February, March, April; the dry season spans the months of May, June, July, August; the wet season 'build-up' months are September, October, November and December.

with *L. longbeachae* (3/6; 50%) ($p = 0.545$), and was the sole method of diagnosis in 1/5 (20%) *L. pneumophilia* and 2/6 (33%) *L. longbeachae* patients. Urinary antigen was positive for *L. pneumophila* in 8/16 (50%) of those who were tested, and was the sole diagnostic means in 5/8 (63%) patients. Three patients with positive urinary antigen had concurrent positive NAAT on respiratory specimen (3/8; 37%).

This study was not designed to evaluate clinical management and therefore data on treatment were not obtained. Standard empiric treatment for Legionnaire's disease in the NT follows national recommendations and includes azithromycin for low-moderate severity pneumonia (three to seven days) or doxycycline (ten to fourteen days) and for patients with high severity disease, azithromycin for seven to ten days.[11]

Discussion

Our study of legionellosis in the NT noted differences in the disease incidence when compared to overall incidence in Australia. Australia has a national incidence of legionella infection of 1.5 per 100,000 population per year.[3] The NT annualised rate over the 11 years of this study, of 2.1 per 100,000 population per year, is 40% higher than the national median incidence. Noting the relative youthfulness of the NT population (legionella infection classically occurs in the elderly), and the dry, arid conditions of the southern half of the NT (*Legionella* prefers a

Table 2: Epidemiological features of patients with *Legionella* infection in the NT from January 2010 to April 2021

Parameter[a]	*Legionella pneumophila* (%)	*Legionella longbeachae* (%)	Total (%)
Number	**21 (41)**	**30 (59)**	**51 (100)**
Median age (IQR)	56 (52–71)	54 (41–65)	54 (41–67)
Sex			
Male	13 (62)	23 (77)	36 (71)
Female	8 (38)	7 (23)	15 (29)
Ethnicity			
Aboriginal and/or Torres Strait Islander	7 (33)	9 (30)	16 (31)
Non-Indigenous	14 (67)	21 (70)	35 (69)
Residence			
Urban	15 (71)	20 (67)	35 (69)
Rural and remote	6 (29)	10 (33)	16 (31)
Seasonality of infection			
Monsoon	11 (52)	12 (40)	23 (45)
Dry	6 (29)	4 (13)	10 (20)
Wet season 'build-up'	4 (19)	14 (47)	18 (35)

a Two cases of *Legionella* infection did not speciate, and are not included in the table.

moist environment), this has significant disease projection implications for future case numbers with an aging NT population. Legionellosis in Aboriginal and Torres Strait Islander persons, who comprise twenty-five percent of the NT population, showed a higher incidence than in non-Indigenous Territorians (2.5 versus 2.0 per 100,000 population per year respectively); the median age of occurrence was 19 years less in Aboriginal and Torres Strait Islander Territorians ($p < 0.01$), which may reflect the known higher rates of health hardware issues in this population.[12] The male predominance of legionella infections (71%) in our cohort, and background rates of lung disease, smoking and comorbidities, are similar to previous studies in New Zealand and Australia.[3,5,13,14] Admission rates to ICU were higher in the NT (13/45; 30%) than in other studies which reported rates of ICU admission up to 16%; this may reflect diagnostic rigour in patients admitted to ICU, who are routinely tested for legionellosis if they have respiratory symptoms.[15] Thirty-day mortality was lower in the NT (2/45; 4%) than the national notified rate of 6%; however, this is within the margin of error for this small sample size.[3] These mortality rates are still lower than the rates reported internationally, with case fatality rates ranging between 8 and 12%; this may reflect differences in the environment and population characteristics as well as increased active case finding in Australasian countries.[16]

Seasonality in NT

Our data showed a trend towards cases occurring in the humid months. Internationally, a striking epidemiologic feature of legionellosis is its seasonality: more cases are reported during the summer.[3,16,17] However, strong evidence indicates that weather—particularly temperature and humidity—drives the summer spike in incidence.[17] Although *Legionella* spp. are common in the environment, dry environments do

Table 3: Clinical characteristics of patients with *Legionella* infection in the NT from January 2010 to April 2021

Parameter	*L. pneumophila* Number (%)	*L. longbeachae* Number (%)	Total (%)
Number	21 (44)	30 (59)	51 (100)
Comorbidities[a]			
Lung disease	4 (20)	15 (56)	19 (40)
Other health conditions	15 (75)	22 (81)	37 (79)
Diagnostic[b]			
Acute serology	10 (83)	19 (68)	29 (66)
Convalescent serology	2 (17)	9 (32)	11 (41)
NAAT positive	4 (80)	3 (50)	7 (64)
NAAT negative	1 (20)	3 (50)	4 (36)
Urine antigen positive	8 (50)	NA[c]	
Urine antigen negative	8 (50)	NA[c]	
Clinical[d]			
Hospitalised	18 (90)	24 (96)	42 (93)
ICU admission	4 (20)	9 (36)	13 (30)
Length of stay (days), median (IQR)	6 (5–10)	6 (4–44)	
30 day mortality	1 (5)	1 (4)	2 (4)

a Comorbidities available for 20/21 *L. pneumophila* and 27/30 *L. longbeachae* cases.

b Acute and convalescent serology performed on 16/21 and 11/21 *L. pneumophila* and 28/30 and 16/30 *L. longbeachae* cases respectively. Nucleic amplification tests (NAAT) performed on 5/21 *L. pneumophila* and 6/30 *L. longbeachae* cases.

c NA not applicable.

d Clinical information available on 20/21 *L. pneumophila* and 25/30 *L. longbeachae* cases.

not support them,[2] and *Legionella* spp. are more sensitive than other pathogens to drying conditions.[1] In contrast, warm and humid weather tends to support pathogen survival, growth, and the potential for aerosol exposures, increasing disease risk.[1] Legionnaires' disease caused by *L. pneumophila* is possibly more common in late summer and early autumn,[17] whereas that caused by *L. longbeachae* peaks in spring and early summer.[13] Most *Legionella* spp., including *L. pneumophila*, mainly reside in bodies of water. Additional factors that promote growth in water include warm temperatures (25 to 42 °C). By contrast, *L. longbeachae* is genetically adapted to invade plant material and primarily resides in soil and compost.[2] Among cases reported in the NT from January 2010 to April 2021, *L. longbeachae* was more common (30/51; 59%) than *L. pneumophilia* (21/51; 41%). This may relate to the environmental conditions that promote survival of *L. longbeachae*.

Diagnosis

The Northern Territory has access to three of the four methods of *Legionella* species diagnosis (culture not available), all of which are complementary. *L. pneumophila* urinary

antigen was the diagnostic in 50% of patients, but is not available for other legionella species. *L. longbeachae* diagnosis was predominantly serological; however, with increasing use of multiplex respiratory NAAT testing, this may alter in the future. No one method meets the requires specificity and sensitivity and our data emphasises the need for a full diagnostic panel if legionella is being considered.

Of the 12 *L. pneumophila* cases diagnosed serologically, ten (83%) were diagnosed from acute sera samples, compared to the 28 *L. longbeachae* that were serologically diagnosed where only 19 (68%) of cases had positive acute serology, and nine patients (32%) subsequently seroconverted. As acute diagnostic specimens are generally taken on presentation to hospital, it may suggest that *L. longbeachae* is a more rapidly progressive infection, and more likely seronegative on acute presentation serology, compared to *L. pneumophila* with a higher (10/12, 83%) rate of diagnosis based on acute serology. However, these findings do emphasise the need for convalescent serology in all undiagnosed pneumonia cases, to improve diagnostic yield.

For three patients, PCR was the sole diagnostic means, but these were all listed as probable cases as PCR diagnosis is not yet defined as a confirmed case in the NNDSS definition but is included in the Public Health Laboratory Network (PHLN) laboratory confirmed definition. The experience in New Zealand[15,18] has shown that NAAT is much more effective at diagnosing legionellosis, in particular because serology is not rapidly available to guide clinical management and because a substantial proportion of patients (20–30%) do not develop detectable antibody response if tested too early in the disease process or at all.[19] Whilst urinary antigen in this study was shown to diagnose 50% of *L. pneumophila* cases (8/16), it is of less utility in the NT context when *L. longbeachae* is the predominant species. Harmonisation of notified and laboratory case definitions would aid in epidemiological research. Greater use of NAAT for diagnosis rather that serology may uncover an increased number of legionellosis cases, particularly *L. longbeachae*, which could allow preventative public health interventions, and more targeted antimicrobial therapy. This was evidenced in New Zealand when active case finding through systematic NAAT testing uncovered an otherwise hidden burden of disease, almost quadrupling the case finding during the period of the study.[18] Active case finding in New Zealand identified that the overall incidence in 20 participating hospitals was 5.4 per 100 000 people per year.[15]

Strengths and limitations

This study has a number of limitations. Firstly, it was a retrospective study, and may have missed cases that did not come through the public hospital system or pneumonic cases that did not have legionella diagnostics performed. Secondly, the diagnostic algorithms in place in the NT are heavily weighted towards diagnosing the common Australian species of *L. pneumophila* and *L. longbeachae*. Other species causing clinical disease may be missed as *Legionella* culture is not routinely performed nor pan-*Legionella* PCR. With the advent of multiplex respiratory PCR, addition of pan-*Legionella* PCR targets may help to characterise the full spectrum of legionellosis in the NT, and as per the New Zealand experience may increase case finding in pneumonia patients. Differences in the reporting definition and laboratory definition mentioned do not change this study's overall conclusions. Finally, this study did not evaluate detailed clinical presentation or individual risk factors for *Legionella* species acquisition (specifically: individual exposures to soil or compost). It also did not evaluate treatment and management of legionellosis and how this influenced hospital length of stay and mortality.

Conclusion

Legionnaire's disease is a serious cause of pneumonia and has a high mortality rate, particularly if it is untreated or occurs in the immunocompromised.[20] The higher incidence of disease in the NT has public health implications, given that the population is younger and relatively

dispersed, which has impacts on access to, and delivery of, healthcare. Reliance on serological testing and urinary antigen in this retrospective study, rather than NAAT detection, means that the true burden of disease may be significantly underreported. Improved clinical recognition and use of diagnostics will allow public health preventative interventions and targeted treatment, and has the potential to improve patient outcomes.

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Author details

Claire Waller[1]
Kevin Freeman[1]
Shereen Labib[2]
Rob Baird[1]

1. c/o Territory Pathology, Building 13, Royal Darwin Hospital, Rocklands Drive, Tiwi, NT, 0810

2. Centre for Disease Control, Building 4, Royal Darwin Hospital, Rocklands Drive, Tiwi, NT, 0810

Corresponding author

Claire Waller

Infectious Diseases Registrar, Royal Darwin Hospital, 105 Rocklands Drive, Tiwi, NT, 0810

Email: Claire.Waller@nt.gov.au

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