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The mysterious illness that drove them to their knees - Ah, that Legionnaires' disease – A historical reflection of the work in Legionnaires' disease in New Zealand (1978 to mid-1990s) and the 'One Health' paradigm

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ABSTRACT

And so, formed the basis for the song Legionnaires' disease (LD) composed by the legendry musician Bob Dylan shortly after this mysterious illness dramatically entered the clinical and epidemiological scene in July 1976 at an American hotel. Now more than forty years have passed since *Legionella pneumophila*, the causative agent of LD, was formally identified in 1977. Once the publicity associated with the outbreak subsided, there was the challenge to science and health professionals of what was an extremely complex and intriguing health concern. In the United States, the outbreak investigation that eventually solved the mystery had taken an array of surprising twists and turns. Globally, it revealed the strengths and weakness of countries' health systems in response to the outbreak from an unknown agent. Extensive international coverage of the outbreak also marked a turning point in journalism's efforts to hold officials accountable for their response to epidemics that had the potential to threaten the lives of hundreds of people. In 1979, New Zealand became an active participant in the international efforts towards increasing the understanding of infection caused by *Legionella* species and set up a centralized laboratory diagnostic service. By 1980 LD had become a notifiable disease making New Zealand one of the first countries globally to do so. This historical narrative in the decade or so from its recognition, provides a unique insight into how the One Health paradigm was instrumental in New Zealand's early response to LD in tandem with control strategies. The findings show that from 1979 the distribution of the *Legionella* species in New Zealand did not follow patterns observed in studies carried out globally.

1. Introduction

One of the most relevant medical discoveries made in the field of bacteriology in the past forty-four years is probably represented by the identification of the *Legionella* bacteria causing the disease legionellosis. As the lyrics of Bob Dylan's song titled 'Legionnaires' disease' suggest, the feeling of confusion that diffused throughout the United States (US) after the 1976 American Legion convention at the Bellevue-Stratford Hotel in Philadelphia left members with a deadly pneumonia (later coined Legionnaire's disease by the media [1] but formally recognized by the CDC in April 1977 as the official name of the epidemic disease [2]), also drove health professionals to "their knees" as they scrambled to identify the mysterious infectious agent responsible for such a lethal outbreak.[1] The reasons why *Legionella* had remained camouflaged before 1976 was primarily by virtue of two iconoclastic traits: (1) it rejected conventional stains used to visualize microbes [3] and (2) its fastidious growth requirements hampered the culturing and detection of the bacteria [2]. Apart from these influences and the emotional response that the 1976 outbreak evoked, there was the challenge to science and health professionals of what was an extremely complex and intriguing health concern. Its discovery in early 1977 emerged when the medical establishment globally (including New Zealand [4]) was nurturing the perception that infectious diseases were largely defeated (due to improved sanitation and the development of effective vaccines and antimicrobial drugs) and that attention and resources should be directed to the more important threat of chronic diseases. The 1976 outbreak challenged the assumption that medical science had closed the book on infectious diseases. It also brought home the importance of public health/medical microbiologists who rather than bowing to received wisdom, trusted their instincts instead [5]. In New Zealand, following the 1976 Philadelphia outbreak astute medical microbiologists and clinicians began to question whether cases of

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[1] 1976 also marked the reappearance of a strain of H1N1 influenza virus, similar to the virus responsible for the 1918 influenza pandemic and Ebola haemorrhagic fever.

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microbiologically undiagnosed pneumonia were *Legionella* infection and that more attention should be paid to determining the aetiology of cases that were not responding to conventional treatment. Initially the difficulty of isolating and culturing the organism hampered the knowledge of its environmental sites, mode of transmission and indirectly the specificity of serological diagnosis. As a result, LD became a classic example of an emerging infectious disease (EID) threat, becoming one of the earliest such diseases to be recognized [6] as requiring a One Health approach. Globally, the approach to reduce the burden of LD demanded an integrated and collaborative process to efficiently and effectively bring together information, capacity, and expertise within and across sectors to protect human health. With the availability of cultures and reagents from the Centers for Disease Control (CDC) (now Centers for Disease Control and Prevention) Atlanta, Georgia in the US soon after the 1976 outbreak, it became possible to establish the testing for legionellosis in New Zealand.

This historical narrative is presented as follows. Firstly, I reflect on the One Health paradigm within the context of EIDs, but here I describe a class of infectious disease, sapronoses in particular one which is not of zoonotic origin but until now has largely been neglected. The One Health approach is much broader than zoonoses alone and a well-known example of a sapronosis pathogen is LD since zoonotic transmission has, to date, not been reported [7]. Secondly, I seek to remedy a historical neglect of LD [6] and go beyond the several published reviews [8–11] that focus on the characteristics of the 1976 outbreak investigation by reflecting on the complexity of responding to this new emerging disease from the perspective of a country outside of the US. In describing the disease's epidemiological features, I delineate through the conceptual lens of the One Health paradigm of public health thinking, how from a very modest beginning New Zealand in 1979 established a Centre for Legionella Reference under the direction of Dr Karl Bettelheim, and surveillance system (which later became highly regarded internationally). I also pay detailed attention to the public and political scrutiny this 'new emerging disease' elicited including a clinical perspective and approaches to control for risk prevention. Data were collected from literature searches and official documents held by Archives New Zealand, including surveillance reports. But official documents convey only part of the story. The strength of popular interest about legionellosis, the curiosity and hysteria that it generated, is most evident in newspaper coverage. Papers from across the country ranging from the *Christchurch Press* to the *New Zealand Herald* (Auckland) carried the most detailed and frequent reports particularly after the 1976 outbreak. Lastly revised drafts of this paper were reviewed by health professionals employed in the sector from the late 1970s until the mid-1990s. The findings are relevant as they show that the distribution of the *Legionella* species (spp.) did not follow patterns observed in studies carried globally from 1979 when the first case was diagnosed in New Zealand. This makes the New Zealand situation worthy of global interest.

2. One Health paradigm in emerging infectious diseases

'One Health' is a relatively new term, however the concept can be traced back to the 1800s [12] although there is no single, internationally agreed upon definition [13]. Nowadays the term is most often used to describe approaches to tackling infectious disease (particularly zoonoses) threats that consider and incorporate all components at different levels of governance, that is, from global to local level, that might lead to, or increase, the threat of disease [14]. These include environmental and ecological components and human factors and for zoonoses, domestic/wild animal factors. Human factors encompass behavioural as well as medical issues, including political and other socio-economic drivers that might result in a disease occurrence or spread [14].

For the purposes of this historical narrative it is a particularly effective approach in deciphering the processes that underlaid the explosive emergence and expression of LD and the need to understand and regulate the environmental context (human-ecosystem interface) onto the global stage. New Zealand's population was just over 3 million at the beginning of the 1980s, (1981 census was 3,175,737) [15] which emerged as a decade of health service reform.[2] In the United Kingdom (UK), United State, the Netherlands, Sweden and many other countries, health services were also either being reformed or policy-makers and politicians were contemplating reform [16]. Public concern about the emergence of a series of novel diseases in the 1970s and 1980s (including LD) that culminated with the global spread of HIV/AIDS, was heightened because of the perception that infectious diseases were previously under control, their often rapid spread and high case fatality rates and because the development of drugs and vaccines to combat some EIDs (e.g. HIV/AIDS) had been slow and costly. As health-care reforms proceeded, various jurisdictions found themselves having to give priority to strengthen partnerships between health-care providers, microbiologists, and public health professionals to detect and control EIDs [14]. As with any EID, international collaboration was therefore deemed essential for One Health implementation since pathogens have no respect for national borders making the health concept more critical. Emergence was also found to be exacerbated by increasing volumes and rates of human travel. The 1976 outbreak was the first formally identified example of travel-associated LD although a retrospective analysis of so called 'Benidorm pneumonia' cases in British travellers to Benidorm, Spain in 1973 and associated in 1974 at the same hotel as the 1976 LD outbreak, suggested that several travel-associated cases were possibly LD [17,18]. Travel is now recognized as a common risk factor for LD. Globally the challenges became immense — from sharing specimens, political sensitivities to international tourism but also resulting in infectious diseases rising back up the health policy and political agendas [19].

3. Recognition of infection

Legionellosis, a set of two respiratory diseases caused by the inhalation of *Legionella* bacteria, incorporates Pontiac Fever and Legionnaires' disease (LD), a sometimes severe and fatal form of pneumonia (including but extremely rare, extrapulmonary infections such as endocarditis). Once the ubiquitous environmental opportunistic bacterium was identified, subsequent antibody testing on old sera revealed that LD was not a new organism with retrospective analysis showing it to be the "*Rickett-like*" organism isolated in 1947 [20]. The organism was also responsible for an unsolved 1957 outbreak of pneumonia [21] and non-pneumonic manifestation of the disease in 1968 in Pontiac, Michigan, later named Pontiac fever [22]. It was also strongly felt that an outbreak of LD occurred in Philadelphia in 1974, in the Bellevue-Stratford Hotel following a convention – the same hotel which in 1976 became ground zero for this deadly bacterium [23]. Since the 1976 epidemic, the genus *Legionella* has expanded extensively so that today it comprises of more than 65 different species, including over 70 serogroups [24] with *L. pneumophila* sg 1 the most prevalent disease-causing variant [25].

Research on LD was initially conducted by the US CDC and post October 1979, also by the US National Institutes of Health (NIH). As their first line of defence against this EID the CDC launched an epidemiological investigation and utilized standard laboratory methodology in their search for the aetiological agent. After *L. pneumophila* was formally identified by CDC microbiologists as the causative agent, the agency researched the biology, immunology and pathogenicity of the organism. The CDC also instituted serologic and pneumonic

[2] A major reform in the 1980s came about through the Area Health Boards Act 1983 which resulted in the decentralization of operational and public health responsibilities away from the Department of Health to regional Area Health Boards.

surveillance and investigated rapid diagnostic techniques. NIH sponsored research was divided into four categories: clarification of the aetiologic niche, understanding of the mode of transmission, delineation of the pathology through the development of animal models and characterisation of different stains and surface antigens in order to develop specific diagnostic tests [26].

Although it is not feasible to pinpoint an exact moment when the enormity of this new disease became apparent, the evolution of emotive language used by the New Zealand media describing LD provides some clues. One of the first articles to appear in New Zealand newspapers occurred on 7 August 1976, under the headline 'Still No Name for Disease', reporting that 'medical detectives' had scored their first breakthrough by almost completely ruling out influenza or swine flu (a relief to health officials who feared it might spread). Instead it was speculated that the mysterious disease may have been caused by a virus or toxin [27], (from fumes from photocopying machines and air conditioning refrigerant decomposition producing phosgene gas [2]) because of the clinical resemblance of the pneumonia to severe influenza [9]. From 12 August 1976 until the end of that year the media amplified the panoply of theories that intensified the hysteria for an aetiology that included nickel carbonyl poisoning [28] (high levels of nickel were caused by contamination from the instruments used during autopsies) [29], heat [30] and bioterrorism or nefarious forces. By the end of 1976 the media were reporting on the 'political theatre' [2] of the November US Congressional hearings which were responding to concern pertaining to the inability of CDC to identify and determine the aetiology of the outbreak. One such melodramatic theory on the disease was captured by *The New Zealand Herald* via a quote from testimony presented by a convention attendee who asserted to having overheard a '*glassy-eyed man mingling with the American Legion members before the deadly outbreak of "legionnaire's disease"…saying: "It's too late, you cannot be saved'* [31]. But these theories did not fit the facts. It was not until 21 January 1977 that newspapers were reporting that the mysterious illness which had been puzzling society for months, was in fact caused by a bacterium [32].

In New Zealand internal administrative structures and funding for addressing legionellosis also emerged as the scope of the disease became better understood. Dr Karl Bettelheim arrived in New Zealand from London to take up a position as scientist (serology) at the National Health Institute (NHI)[3] the same year as the Philadelphia LD outbreak. In 1979, drawing from his experience in medical microbiology, Dr Bettelheim was instrumental in setting up a LD Reference Laboratory for New Zealand within the Reference Immunology Section at the NHI. The following year Dr Bettelheim recruited microbiologist Annette Chereshsky to the LD Reference Laboratory, who as like himself was a member of a remarkable group of émigrés from Europe who contributed greatly to the reshaping of microbiology, virology and environmental health in New Zealand in the years post World War Two. In 1992, the New Zealand Communicable Disease Centre (formerly the NHI) became part of the Institute of Environmental Science and Research Limited ("ESR"), a Crown Research Institute. Today the LD Reference Laboratory continues to provide a supplemental diagnostic, confirmation and characterisation service for clinical and environmental specimens and isolates for much of New Zealand.

The progress of identifying LD in New Zealand was directly proportional to the number of collaborations. For example, results with patient sera only became significant when linked with the comprehensive epidemiologic information generated by others. Dr Bettelheim recognized that as a diagnostic centre for *Legionella* for New Zealand laboratories, it was important that results of patient sera obtained by the NHI correlated with those obtained from CDC whose microbiologists had discovered the bacteria in 1977. The US CDC served as a national reference facility and accepted specimens from state and, Federal facilities and under special circumstances from institutions from outside the US. From 1979, laboratory diagnosis in New Zealand depended mostly on the Indirect fluorescent antibody (IFA) test which had also become the method of choice of all LD reference laboratories throughout the world. The IFA test first described by McDade et a1. [33] was used because of its sensitivity and specificity particularly as Wilkinson et al (1979) [34] from the CDC were able to develop and define standardized reagents and procedures for the test. This enabled the NHI to apply a single set of diagnostic criteria for minimum positive titres which was contrary to what was happening in other countries who having taken up the IFA test, had developed their own methods leading to disparities [35,36] in their results. Initially the IFA test was performed on sera submitted to the NHI mainly from hospitals using only *L. pneumophila* sgs 1–4 as antigens. Gradually as new species and serogroups emerged from the CDC or the American Type Culture Collection, further antigens were brought into use so that by the beginning of 1986 there was a battery of 19 different heat-killed antigens which were combined into five pools [37] (Table 1). CDC supplied the antigens to New Zealand (which necessitated permits from the then Ministry of Agriculture and Fisheries for their importation) for *L. pneumophila* sg 1–4; the remaining 15 antigens were prepared at the NHI in accordance with methods recommended by the CDC [38] or Legionnaires' disease reference laboratory (LDRL) (Dr Paul Edelstein) in Los Angeles, US [37]. Control sera that was used in the IFA test were supplied partly by the CDC or obtained from hospitalized patients suspected of suffering from LD. Selected titres of the latter were referred to the CDC for quality control purposes. Nevertheless, it was recognized that the IFA test was not the easiest serologic test to perform and that there is a measure of subjectivity in reading the degree of fluorescence (unpublished correspondence). In addition, with the discovery of new serogroups of the LD bacterium there was an increased need not only for an easier, less subjective test than indirect immunofluorescence but for a test using some form of "group" antigen, which would reduce the considerable labour involved in diagnosis.

Of the other tests, Bettelheim contacted the CDC to enquire about the findings from a published article on a simpler but less sensitive test to the IFA test in which the authors' used a microagglutination technique to detect antibodies to *L. pneumophila* [39]. He was particularly interested in ascertaining whether it might replace the IFA test since as the NHI was sending representative sera to the CDC for confirmation of their IFAT results he did not want to alter the NHI methods without consulting CDC first. Specimens were also examined by the Direct Immunofluorescent Assay (DFAT) using reagents which were partly obtained commercially and partly prepared at the NHI (unpublished correspondence). Absorbed pools containing antisera against thirty-three *Legionella* spp. (including serogroups) and used in the slide agglutination test were prepared at the CDC and kindly donated to the NHI [37]. Diagnosis was improved significantly using this technique, because the diagnosis could be made 2 to 7 days after onset of symptoms, compared with the 3 weeks often necessary for a four-fold rise in indirect immunofluorescent titre to occur [40]. The diagnosis of LD was also confirmed by culturing the organism using techniques and media based on a manual developed by Edelstein [41]. The materials for culture were mainly lower respiratory tract fluids, biopsy and necropsy specimens. Culturing techniques and media used were as recommended by the US CDC.

[3] The NHI was initially located within Wellington city (New Zealand's capital) but was moved to a new complex of laboratories and servicing facilities at Kenepuru in 1982 on the outskirts of Porirua, north of Wellington. The NHI also comprised of five other regional laboratories located in the microbiological departments of public hospitals in Auckland, Hamilton, Napier, Christchurch and Dunedin. In the last few months of 1989 the NHI was changed to the New Zealand Communicable Disease Centre (CDC) possibly in the image of Communicable Disease Center (CDC) in the US.

Table 1
Year antigens brought into use in New Zealand – legionella indirect fluorescent-antibody (IFA) pools [37].

Legionella species and serogroup (sg)		Year antigen brought into NZ	CDC Strain Designation	No of Positive Cases			
				1982 (n = 561)[a]	1983 (n = 901)[a]	1984 (n = 1218)[a]	1985 (n = 1733)[a]
Pool A	*L. pneumophila* sg 1	1982	Knoxville-1; Philadelphia-1	5	3	4	6
	L. pneumophila sg 2	1982	Togus-1	0	1	4	1
	L. pneumophila sg 3	1982	Bloomington-2	0	0	1	0
	L. pneumophila sg 4	1982	Los Angeles-1	2	1	1	2
Pool B	*L. pneumophila* sg 5	1983	Dallas-1E	0	2	0	1
	L. pneumophila sg 6	1983	Chicago-2	7	16	32	53
	L. pneumophila sg 7	1985	Chicago-8				0
	L. pneumophila sg 8	1985	Concord-3				0
Pool C	*L.dumoffii*	1984	NY-23 Tex-KL			2	3
	L.gormanii	1984	LS-13			0	2
	L.jordanis	1984	BL-540			7	15
	L.micdadei	1983	TATLOCK		10	5	14
Pool D	*L.feeleii* sg 1	1985	WO-44C				4
	L.oakridgensis	1985	Oak Ridge-10				0
	L.sainthelensi	1985	Mt St Helens-4				13
	L.wadsworthii	1984	Wadsworth 81-716A			0	2
Pool E	*L.bozemanae* sg 1	1984	WIGA			1	1
	L.longbeachae sg 1	1984	Long Beach-4			10	6
	L.longbeachae sg 2	1985	Tucker-1				3
Mixed				0	13	13	14
Total				14	46	80	140

[a] No. of sera examined.

4. Epidemiological features

At the beginning of 1979, countries outside of the US in which sporadic cases LD had been identified were: UK, The Netherlands, Denmark, Canada, Sweden, Israel and Australia [42]. Twelve months after the *L. pneumophila* was first identified in 1977 in the US, the first report about LD appeared via two editorials in the *New Zealand Medical Journal* published in January [43] and September [44] 1978. These editorials described the pattern of the disease that was emerging globally including that it was an airborne infection and person-to-person infection appeared unlikely (despite a possible patient-to-doctor transmission of LD reported in *The Lancet* in December 1978 [45]; more recently the first evidence of human-to-human *L. pneumophila* transmission was reported [46]). With many travellers going to the US and Europe it was surmised that sporadic cases would eventually turn up in New Zealand [44]. Epidemiological analysis of epidemic and sporadic cases identified a variety of further risk factors for the development of LD or for fatal infection. Notable amongst these were smoking, increased age (although pediatric infections had been described [47,48]), chronic lung disease and immunosuppression. It soon became apparent that a combination of risk factors produced the highest probability of infection: decreased host defenses and exposure to an environmental source that was disseminating the bacteria [9]. The epidemiological investigation led by David Fraser of the US CDC into the 1976 LD outbreak suggested the disease was most probably spread by the air borne route [49] but the ubiquitous presence of *Legionella* spp. in the environment was not fully known until 1980. By 1981 evidence for confirmation of human exposure to LD via an airborne route was obtained [50] through inducing experimental respiratory infection in guinea pigs and rhesus monkeys using a strain of *L. pneumophila* that was isolated from a contaminated domestic water supply.

In 1979 the NHI provided the back-up for New Zealand's first occurrence of *L. pneumophila* infection via serological immunocytological and histological techniques and was reported in the *New Zealand Medical Journal* [51]. This was quickly followed by another serologically confirmed case documented in the same journal which occurred on 18 January 1980, when the Christchurch Public Hospital notified the then Department of Health that a 29-year-old female nursery assistant with a five-year history of polymyositis had been admitted to hospital with pneumonia. Rising serum antibody titres confirmed a diagnosis of LD. As a result, infection with *L. pneumophila* became an important consideration in New Zealand when patients presented pneumonia and severe pyrexia symptoms especially if they showed known independent risk factors including smoking and alcohol abuse or were over the age of 40 [52].

With the increased availability of laboratory methods capable of confirming the diagnosis it became apparent that sporadic cases of LD were more common than epidemic cases. Yet the need for a surveillance system was based on the premise that outbreaks, as opposed to sporadic cases could arise from common environmental sources. Failure to detect LD as early as possible could bring justifiable criticism on health agencies and as the disease was now in the public eye, draw political criticism particularly if an outbreak were to affect a major tourist facility. Reports of two sporadic cases of LD in the early 1980s drew attention to an association with recent travel [53,54]. The New Zealand LD surveillance system was established in 1980 when the Government acted to change the existing legislation making legionellosis a notifiable disease - one of the first countries globally to do so.[4] This occurred on 12 June 1980 in addition to other EIDs namely *Campylobacter* infection and Ross River Fever via the Infectious Disease Order 1980/111. Only those cases of Legionellosis (in which there was a typical clinical illness and a confirmatory positive antibody blood test) that were notified to the Medical Officer of Health by a medical practitioner, were investigated. The criteria for confirmation of a positive case in patients with clinical manifestations was based on: 1) a four-fold or greater rise in IFA titre to ≥ 1:128; 2) a single or static titre of ≥ 1:256 when the clinical findings were compatible with current legionellosis; 3) demonstration of the agent in lung tissue, respiratory secretion or pleural fluid by the DFA test; or 4) isolation of the agent from lung tissue, respiratory secretions or pleural fluid [37]. With advances in diagnostic testing methods and a better understanding of background antibody titres from seroprevalence studies, the case definition evolved over

[4] Countries that followed mandatory notification of LD included Norway (Norwegian Surveillance System for Communicable Diseases 1980); Ireland (Infectious Disease Regulations 1981); Scotland (Public Health (Notification of Infectious Disease (Scotland) Regulations 1988); France (added to the list of notifiable diseases set out in the French Decree of January 1960 in 1987).

Table 2
Reported incidence of LD in several countries (1978–1986) (Adapted from Bhopal, 1989 [64]).

Reference (year)	Country of origin	Study period	Serology description	Estimate of mean annual incidence per million population	Criteria
Centres for Disease Control (CDC), 1988 [65]	United States	1978–1986	CDC reagents	3.0	CDC criteria
Chereshsky, 1986 [37]	New Zealand	1982–1985	CDC reagents and methods	10.6[a]	CDC definition
Committee of Inquiry, 1987 [66]	England	1978–1986	Mainly formalized yolk sac antigen to range of antigens as discovered	3.1	Case definition on same principles as CDC guidelines
Fallon (various years) [60,67–72]	Scotland	1978–1986	1978 – CDC reagents; subsequently heat-killed antigens to range of species and serogroups as discovered	9.5	Case definition similar to CDC guidelines
Rosmini, 1984 [73]	Italy	1979–1982	CDC and PHLS reagents. Most cases diagnosed on serology	0.5	198 cases; 32 were clinical diagnoses and single IFAT titre of > 128 accepted. Validity of estimate poor
Heltberg, 1988 [74]	Denmark	1982–1985	Heat killed antigen from 13 species or serogroups	2.9[a]	CDC criteria on serology used. Five cases had no pneumonia; 37 cases were non-*pneumophila* but diagnosed serologically

[a] Denotes incidence when non-*L. pneumophila* cases, with only serological evidence, are excluded. When such cases were included the incidence was 6.0 in Denmark and 28.1 in New Zealand.

time.

In the early 1980s there were no detailed figures for the incidence of *Legionella* generally in the New Zealand population. This is because nobody had yet had the opportunity to study population samples with available antigen (Lpsgs1 to 4). Examination of sera from healthy blood donors (Otago/Southland and Hamilton) by the NHI in 1981 for antibodies to *L. pneumophila* sg 1 showed that these levels were widespread and significant (level of exposure in the order of 2% [55]) amongst healthy people (with higher levels of antibodies in the < 40 age group reflecting a degree of immunity to *Legionella*) suggesting that the organism may also be widespread throughout New Zealand. This was consistent with several reports in the scientific literature at the time which suggested that the organism was not solely an opportunist which attacked compromised victims primarily in hospitals [56].

Few studies on the incidence of LD in spatially defined populations appeared in the literature. Further, the comparability of the studies was low. Table 2 summarizes some published data from the 1980s on the incidence of LD in several countries; globally incidence varied greatly but was significantly elevated for New Zealand. Based on routine surveillance reports, the mean annual incidence rate in New Zealand was 10.6 per million population (using Lp species only) [37] (Table 2). It is noteworthy that both New Zealand and Scotland which, at that time, had similar-sized populations, climate and health service have similarly higher incidence rates than other countries such as the US, Denmark, England and Italy (Table 2). Whether the comparatively high incidence was due to more case ascertainment by clinicians or a better surveillance system (or both) or reflected a truly higher risk remains unclear. The presence of a central reference laboratory providing an accessible service may have promoted an awareness of the disease in New Zealand and allowed comparatively good surveillance (which consisted of both laboratory confirmation and notification). The NHI was in a unique position to establish a protocol for the investigation of legionellosis. It had the resources of a serology unit with scientific staff who were highly motivated and skilled that kept up to date with emerging overseas developments in the laboratory diagnostic field, and initiated approaches to CDC as soon as test reagents became available.

A review of LD cases diagnosed in 1,246 patients from 1979–1988 found that of the 244 cases attributed to *L. pneumophila*, 167 (68.4%) were caused by serogroup 6. Of the 249 patients with significant antibody levels to other *Legionella* spp., the predominant species were found to be *L. micdadei*, *L. longbeachae* sg 1 and 2 and *L. jordanis* [57]. These results derived predominantly from serological investigations were suggesting the possibility of a different profile for New Zealand compared with many international studies which suggested that LpSg1 was the main cause of legionellosis (Table 1) [57,58]. Species or serogroups frequently encountered included LpSg6, *L. micdadei*, *L. jordanis* and *L. longbeachae* sg1 although regarding the latter three species, it was recognized that the small numbers of cases associated with non-*L. pneumophila* species thus far limited further epidemiological evaluation. An US study of 530 specimens from the human respiratory system by DFA staining yielded 63 positive specimens with legionellae but only two of these belonged to sg 6 [59]. Similarly, sera from 86 cases surveyed in Scotland from 1977–1981 by IFA techniques demonstrated only one example of seroconversion to sg 6 [60]. This confirmed the theory that different geographical areas may have different species/serogroup distributions [61]. However, although this study provided data on the relative seroprevalence and importance of the different *Legionella* spp. in New Zealand there was also emphasis placed on the need to utilize culturing techniques [37]. This technique allows establishing the relationship between strains isolated from environmental sources and those isolated from affected patients [62]. Table 3 shows a possible correlation between *Legionella* spp. isolated from clinical and environmental sources between 1979–1989) as reflected in seropositivity as well in those implicated in case fatalities. Table 3 shows that Lp Sg1 and 6 was the most frequently isolated *Legionella* serogroups from clinical (76.5%) as well as all environmental (61.3% of 921) samples. The latter

Table 3
Prevalence of *Legionella* spp. in New Zealand (1979–1989) [57].

Legionella spp.	Clinical Isolates (n = 17)	Environmental Isolates (n = 98)	Implicated fatal cases (n = 23)	Identified by IFA (n = 244)
Legionella pneumophila				
Lp sg1	8	32	9	31
Lp sg6	5	25	7	167
Total	13 (76.5%)	57 (61.3%)	16 (69.6%)	198 (81.1%)

Non-*Legionella pneumophila*	Clinical Isolates (n = 13)	Environmental Isolates (n = 5)	Implicated fatal cases (n = 9)	Identified by IFA (n = 249)
L. micdadei	–	–	6	69
L. longbeachae sg1	1	1	1	69
L. longbeachae sg2	1	1	1	63
Total	2 (15.4%)	2 (80%)	8 (89%)	201 (80.7%)

Table 4
Diagnostic tests used to confirm LD fatalities in New Zealand (1979–1989) [57].

Diagnostic Test	Number of Deceased Patients (1979–1988)
Culture only	2
Culture and serology	5
DFA (lung tissue)	11
DFA and seroconversion	4
DFA and high titre	3
Positive serology – seroconversion	6
Positive serology – high titre	2
Total	**33**

were performed by NHI between 1986 and 1989 at the request of various interested parties from throughout New Zealand possibly in response to a defining moment during 1985 in Wellington (see below) namely the global outbreaks which were being reported in the media. Most of the samples were taken from cooling towers used for industrial purposes (11% positive from 557 samples tested) and for air conditioning (11.5% positive from 243 samples tested). These two serogroups (Lp Sg1 and 6) were also both responsible for causing deaths in New Zealand. However, the case fatality rate was difficult to assess because the outcome of the patients' disease was not always made known to NHI. Table 4 shows that at least 33 patients who died following pneumonia had laboratory-confirmed legionellosis. The age and sex distribution of positive cases followed the pattern of prevalence in males observed internationally: 70.7% of patients were males who showed increased incidence with age – 41.1% of the patients were over sixty years of age. Though sporadic positive cases occurred evenly throughout the year, there was a seasonal variation similar to that of epidemics. The seasonal distribution of the isolated Legionellae from environmental samples was slightly higher during the autumn and winter, in contrast to other countries. This is due to New Zealand's unique climatic factors namely its temperate, humid and windy conditions making it ideal for the bacteria to survive and facilitate aerosol transmission [63].

Despite the dramatic increase in global knowledge since the 1976 Philadelphia outbreak, a major perplexing question about the epidemiology of legionellosis remained – the reason for the difference in the epidemiology of Pontiac fever and LD. At the beginning of 1986 Bettelheim wrote to Dr Paul Edelstein (LDRL) seeking assistance with interpreting mild cases of *Legionella* (thought to be Pontiac fever) from two patients whose sera had a high titre to *L. pneumophila* sg 6. Both these sera were obtained from people whose clinical presentation did not include pneumonia. He reported that New Zealand had several similar cases, who had seroconverted from 1:64 to ≥ 1:512 to one or more of the test antigens (unpublished correspondence). Edelstein responded by indicating that determination as to the significance of seroconversion without pneumonia required prospective studies (unpublished correspondence) which had not been undertaken in New Zealand but were to come later.

5. The clinical perspective

From the clinical perspective LD was first and foremost a new form of pneumonia [6] in which several clinically important points were gradually reinforced through published case descriptions. Pneumonia, a common disease which was once regarded as 'the captain of the men of death' [75] because of its association with significant mortality had become treatable with the introduction of antibiotics such as penicillin and other antimicrobial drugs, resulting in greatly improved survival rates [25]. This led to bacteriological expertise and clinical interest in the disease to decline precipitously [76]. LD was occurring sporadically in previously healthy persons, not only nosocomial patients and immunocompromised persons [77]. There were three common denominators associated with LD that were problematic: 1) it did not have any features that could distinguish it either clinically or radiographically from other types of pneumonia rendering a diagnosis based solely on clinical findings untenable. Instead specialized diagnostic tests (serologic study, direct immunofluorescent antibody examination, selective culture) were necessary to confirm the presence of this disease 2) these laboratory tests were difficult and slow. Because many new serological groups of *L. pneumophila* and other *Legionella* species had yet to be described (to this day species are still being discovered for example two species in 2016 [78,79]) clinicians needed to suspect and provide treatment for LD in the clinical setting, regardless of negative laboratory test results; and 3) penicillin which was the accepted drug of choice for the treatment of pneumonia was ineffectual against *Legionella* spp. Yet early trials showed that prompt therapy using other antibiotics such as erythromycin was efficacious in reducing the case-fatality rate among patients with LD [80]. Newer agents have since replaced erythromycin, the historic antibiotic of choice, as preferred therapy. More recently fluoroquinolones and the newer macrolides (clarithromycin, azithromycin, roxithromycin) are found to be more active than erythromycin in vitro and intracellular assays [81]. Nevertheless, while the prognosis was actually quite good; the lingering question for clinicians was when to use erythromycin [6]? For example, in 1990 two cases of sporadic community-acquired dual infection with *L. pneumophila* and *M. pneumoniae* organisms were described. Although erythromycin was known to be effective against these two bacteria, LD required an extended and larger dose of erythromycin. Therefore, a correct differential diagnosis of those infections was regarded as vitally important [82].

A frustration for clinicians related to the technical difficulty in obtaining appropriate specimens which influenced the choice of antibiotic therapy and patient outcome. In the early days in New Zealand, the identification of *Legionella* spp. by serological methods was the most frequently used technique. Serological evidence of current *Legionella* infection was based on seroconversion, or at least a four-fold increase in titre between acute and convalescent sera. When the first serum sample is taken late post-onset of infection, the seroconversion may have already occurred. In such cases no four-fold increase in titre could be

demonstrated and patients with high (≥1:256) but stable titres had to be reported as presumptively positive. In 1986, 304 (24.1%) of patients with clinical manifestations suggestive of current *Legionella* infection were reported as presumptively positive. Because of awareness of LD among clinicians in New Zealand was still very low, in most of these 304 cases the first serum sample to be tested for legionellosis were taken during the convalescent stage of the illness [83]. Of note too was the difficulty in identifying with any certainty, an aetiological agent based solely on serological results alone (a positive antibody test does not per se indicate acute infection), and that further work was required that placed more emphasis on culturing techniques [37] due to the occasional occurrence of false-negative immunologic tests [84]. To encourage cultural diagnosis of LD, in 1984 a letter was published in the *New Zealand Medical Journal* acknowledging the clinical isolation of *L. dumoffii* from a sputum sample at NHI and four strains of *L. pneumophila* (three sg1 and one sg4) were isolated from clinical specimens at the Auckland Hospital and confirmed at NHI [85]. In that same year, the "*Legionnaires' Disease Laboratory Manual*" published by Dr P H Edelstein (LDRL), was obtained. Based on Dr Edelstein's recommendations several changes were made in the NHI's Methods Manual particularly regarding *Legionella* isolation and identification. To gain further knowledge and expertise in the workings of a complex and ever-changing field of diagnostics Annette Chereshsky was sent to work alongside microbiologists located at CDC in Atlanta, Georgia and LDRL, Los Angeles in 1986. Both organizations were recognized internationally as authoritative in legionellosis and New Zealand communicated with them regularly. In 1988 the NHI in turn provided training courses for hospital medical technologists from throughout New Zealand. The courses were designed to provide a theoretical and practical experience in methods for isolating legionellae from clinical and environmental specimens, as well as in methods for diagnostic serology [57].

But it would be several years before hopes of a simple, specific, sensitive and well validated rapid diagnostic test would become available. Early studies on a 'new' antigen detection in legionellosis patients were reported at the Second International Legionella Symposium in Atlanta in June 1983 [86]. This led to the development of a commercial enzyme immunoassay for urine specimens, later manufactured and distributed by Binax, Inc. (Portland, Maine) [26]. This kit was sold in New Zealand and incorporated during the early 1990s into the suite of tests used to detect the presence of *Legionella* bacteria (serology, culture, DFA). However, it was recognized that while this test has very good specificity and sensitivity, it only detects infections with LpSg1. This made the test of limited use for the diagnosis of legionellosis in New Zealand, especially when more than 50% of diagnosed cases are caused by *Legionella* species other than LpSg1 such as *L. longbeachae* [87].

During the 1980s, the international classification of pneumonia based on lists of different pathogens was abandoned in favour of a more practical classification that helped to guide investigation, management and therapy: community-acquired pneumonia (CAP), hospital-acquired or nosocomial pneumonia, and pneumonia in the immunocompromised host [88]. Pneumonia in New Zealand was becoming a topical and perplexing subject. According to the National Health Statistics Centre's "Mortality and Demographic Data", about half of 3,700 cases of pneumonia in 1981 in New Zealand were caused by an unspecified agent [89]. Pneumonia was identified as the fourth most important cause of mortality in New Zealand at that time. Prospective studies on the aetiology of sporadic pneumonia in New Zealand were encouraged to ascertain the proportion of pneumonia attributed to *Legionella* [58]. Between 1982 and 1983 the British Thoracic Society undertook a prospective study of CAP in adults of 25 British hospitals and in the process developed a prognostic index evaluation [90]. Yet, a prospective study on the frequency of *Legionella* infection as a cause for CAP did not occur in New Zealand until the end of the 1980s [91]. In that study *L. pneumophila* accounted for 4% of CAP which was higher than the comprehensive British study [90]. A later study showed that a diagnosis determined serologically of *Legionella* infection was a relatively common cause of CAP (11%) [92]. The high rate may in part have been due to particular attention being directed towards detection of *Legionella* spp. at that time [92]. It was also noted that a range of *Legionella* spp. other than *L. pneumophila* had caused a significant percentage of infections which had been observed previously [37].

6. Approaches to control - guidelines and regulations for risk prevention

In common with controlling most public health issues, understanding the epidemiological features of legionellosis was a critical step in designing and adopting preventive measures for reducing the risk of disease transmission. Risk management strategies for *Legionella* followed a One Health approach and incorporated a multiple barrier approach aimed at controlling the growth, survival and dissemination of the bacteria.

The 1976 LD outbreak led to many changes. Evidence was obtained implicating a cooling tower in the transmission of legionellosis via aerosolization of the disease-causing bacteria in water droplets, leading to illnesses among those who inhaled large amounts of droplets containing the bacteria. This realisation led to changes in routine maintenance procedures for many aerosol-producing devices such as cooling towers, spas, and respiratory therapy equipment to limit growth of the *Legionella* bacteria. The development of prevention strategies is an ongoing process involving medical professionals, engineers, and chemical disinfectant manufacturers.

In New Zealand the first advice given to health professionals came from the then Department of Health which issued a Circular Memorandum (CN 1980/141) that outlined the environmental risk factors associated with LD. On 5 December 1980 an unnumbered Information Circular was also sent to all medical officers of health entitled '*Air Conditioning Maintenance and Health*' that discussed LD and humidifier fever (an influenza-like illness resulting from exposure to moulds growing in humidifier systems) and recommended action at the district level. The gradual increase in the number of sporadic cases in the Wellington area since the disease became notifiable in 1980 and belief that the mysterious LD was spread via air conditioning systems prompted the Wellington City Council to undertake a survey of eleven buildings across the city in 1982. This investigation followed a question posed by a councillor (also a GP) at a Council meeting as to whether there was any evidence linking the systems with the disease [93]. Water samples from eight of the eleven cooling towers tested using monoclonal antibodies specific to *L. pneumophila* sg 1 were positive. Despite this sample size being very small, it nevertheless indicated the presence of this particular strain in the New Zealand environment raising speculation by Chereshsky that it '*probably means that it is our turn for a big outbreak is yet to come*' [57]. While outbreaks of LD were being widely publicized globally from common environmental sources, New Zealand did not experience its first identified outbreak until 1990 which was associated with a cooling tower [94,95] (although a cluster of suspected *Legionella* infections in male patients at a psychiatric hospital north of Wellington was described in 1987) [96]. But knowledge of the epidemiology of LD was incomplete. It was understood by 1981 that the presence of the bacteria in an aquatic environment and warm water temperature were two factors that could increase the risk of LD. The third component was yet to come – the discovery of the role of amoebae in the environmental ecology of *Legionella* spp. Several investigations had determined that Legionellae could survive within biofilms in building water systems [25]. Such a consortium of microorganisms in a biofilm helped to explain the erratic phenomena of some overseas LD epidemics, based on sloughing of the biofilm in response to physical or chemical change [2]. Accordingly, it was not possible to give precise guidance on action which might be taken to prevent outbreaks of the disease or after one or more cases had occurred. Further programmes designed to keep hospital water supplies free from contamination at all

times would have been economically impracticable. For the present, guidance was limited to those measures which might be taken to reduce the chances of a LD outbreak occurring.

During the period 1976 to 1982 there were several multiyear outbreaks of LD in the USA particularly outbreaks of nosocomial LD, the best example being the Los Angeles Wadsworth Veterans Administrations Hospital, which was the site of a continuing outbreak due to contaminated potable water from 1977 to 1982 [97]. On this basis the mysterious nature of LD was making good television. During 1983 the American medical drama '*St Elsewhere*' was aired on New Zealand television in which an attempt at controlling a hospital epidemic of LD was depicted in two episodes. Although it was only a television series that influenced public perception of medical practice [98], it was based on the reality of a potentially serious situation of LD had since after all it had been identified in New Zealand. In a bid to address the increased risk of incidences of litigation, US principals of companies in New Zealand were also making inquiries to the Department of Health as to what measures were being taken to ensure the wellbeing of occupants in office buildings. Faced with competing priorities and the fact that New Zealand had not experienced an outbreak of LD, setting up monitoring system for cooling towers was going to be a major undertaking well beyond the resources there were available to the NHI and as such was not warranted as a high priority (unpublished correspondence).

From April-May 1985, a UK outbreak (deemed the world's largest at that time) at the Stratford District General Hospital was a defining incident which brought together the medical, social and political dimensions of LD in New Zealand. Media interest was stalwart because of its high fatality rate (36%) and the fact that outbreaks were occurring where they were least expected (or wanted) for example vulnerable hospital patients. The epidemic strain of LpSg1, was isolated from the cooling water system of one of the hospital's air conditioning plants [99]. There was a far more high-profile incident following the positive identification of *L. pneumophila* in the cooling water section of the New Zealand Parliamentary Executive building (informally referred to in New Zealand as the Beehive due to its distinctive shape) air conditioning system. This followed the revelation via a coronial investigation that parliament's then former Speaker of the House had died from pneumonia caused by a strain of *L. oakridgensis* (confirmed by CDC, May 1985) but not from the strain found in the Beehive basement water storage tank. This was because LpSg1 had not come into contact with the circulating air [100]. At the time it was considered that this was only the second confirmed human infection globally from *L. oakridgensis*, the first one having occurred in Canada [101]. The former Speaker's immune system was impaired because of chemotherapy for stomach cancer and therefore at risk of contracting an opportunistic infection like *Legionella* [102]. Immunosuppression is now known to increase susceptibility and is a risk factor for the disease [103].

The political events relating to the discovery of *Legionella* bacteria within the confines of Parliament Buildings also coincided with demands from NZ Public Service Association (PSA) in response to concern from staff that they were working in an area suspected of being a health and safety hazard and in part by media publicity, that all government buildings should be tested for the bacteria (unpublished correspondence). To abate this concern the Department of Health initiated a survey to determine serological levels of Beehive staff and politicians, who had no history of clinical legionellosis, on random sampling compared with matched sera held at the NHI serum store. The findings exposed the potential risk to employees and politicians revealing several of those tested showed previous exposure to the organism but did not show when or how the infection occurred [104]. In addition, regular testing was carried out and procedures were implemented to ensure that all static water supplies/air conditioning systems in the parliament complex were regularly checked [105].

This incident and the survey of buildings undertaken by the Wellington City Council in 1982, lent urgency to the need for action nationally to ensure steps were taken to control the growth of microorganisms or other contaminants in plumbing or air conditioning systems where *Legionella* presented a health risk. In June 1985 the Department of Health issued guidelines to all designated Medical Officers of Health and hospital Medical Superintendents nationwide for the investigation and control of outbreaks of legionellosis [106]. Following this in 1987 "*The Code of Practice for the Control of Hygiene in Air and Water Systems in Buildings*" (NZS 4302:1987) was published to provide advice aimed at reducing the risk of *Legionella* in building water systems. In developing the standard, consideration was given to the latest advice internationally. By coincidence the standard was released at the time of the major outbreak in Wollongong, Australia in 1987. This was Australia's largest outbreak of LD recorded at that time in which forty-four cases were diagnosed of which there were nine deaths. The organism responsible for that outbreak was LpSg1 and a cooling tower was deemed to have been the source of the epidemic [107]. The Standard was written at the request and funded by the Department of Health. This was augmented further by another departmental circular memorandum to all hospitals, Area Health Boards and district offices. The circular highlighted the need to ensure that local authorities understood that the design and function of air and water distribution systems in buildings could affect the potential health risks posed by *Legionella*. In 1988, two local authorities Rotorua District and Wellington City Councils developed bylaws through provisions in the Health Act 1956 which made it a mandatory requirement for any air conditioning cooling tower system installed in industrial, commercial and residential accommodation buildings to be designed, installed, commissioned, operated, and maintained in accordance with the requirements of the NZS 4302: 1987 standard. The bylaws have been superseded by more recent building related legislation also administered by local authorities, aimed at ensuring testing for *Legionella* bacteria takes place on a regular basis to prevent its growth particularly in cooling towers [90]. In 1991 the need to revise the 1985 guidelines on the prevention and management of *Legionella* outbreaks was recognized and a workshop entitled "*Control of Legionella in air and water handling systems*" was convened in Wellington, New Zealand. The *New Zealand Guidelines for the Control of Legionellosis* published in 1995 were based on 1989 guidelines issued by the Victorian Department of Health [108], incorporated recommendations made by the workshop participants. These guidelines have subsequently been revised by the New Zealand Ministry of Health (former Department of Health) to account for more recent research about the hazards associated with the bacteria, the management of potential sources of *Legionella* and reporting and investigation of cases [109].

7. Conclusion

This historical reflection of a sapronosis namely LD in New Zealand provides a powerful illustration of the One Health paradigm that manifested itself at the local, national and international level over the last quarter of the twentieth century. What started out as a local disease outbreak in a Philadelphia hotel quickly became global headlines - '*the epidemiological story for the decade and one of the major epidemiological events of the century.*' [110] Medically LD was a new type of pneumonia which if not carefully managed had the potential to be a public health hazard thus necessitating a centralized diagnostic testing and surveillance regime. Politicians were reeled into controversies surrounding LD when the bacterium was revealed as the agent responsible for the death of the New Zealand parliament's Speaker of the House in 1985. This together with widely publicised point source outbreaks outside of New Zealand, some of which included hospitals, served to keep the condition continuously on the media radar and the wider public domain. For public health engineers the uncovering of environmental sources of *L. pneumophila* bought into prospect a means of control, in turn resulted in the establishment of national standards in respect of air-conditioning systems. This was all set within a new culture of health and safety

practice. As certainties about LD accumulated the areas for doubt were, at least, becoming more clearly defined.

The initial descriptions of legionellosis provided a powerful illustration of the One Health paradigm in the multifaceted collaboration between microbiologists, clinicians, hospital laboratories, public health agencies and local government. This was the key ingredient in the saga of LD that unfolded at the international, national and local levels. At the international level the American CDC, because of their role in the discovery of the bacteria, became the global reference centre for the diagnosis of LD cases and their review of stored specimens in laboratories which revealed earlier outbreaks of the disease and sporadic cases dating back to the 1940s. They showed that the infection was not new but had escaped recognition because the causative organism did not grow on conventional culture media used to grow bacteria in the hospital laboratory. In New Zealand, the role of establishing the surveillance and diagnosis of legionellosis at a national level was led by pioneering medical microbiologists Dr Karl Bettleheim and Annette Chereshsky who kept abreast with emerging trends internationally in laboratory diagnostics and initiated CDC approaches once reagents became available. From 1979 when the first New Zealand LD case was reported, they were instrumental in publishing several reports establishing that the disease was widespread and regularly notified. They were able to demonstrate that New Zealand did not follow findings being reported overseas. Dr Edelstein was to observe *that Legionnaires' disease in New Zealand is not uncommon* and that a new species in New Zealand was eminent - *I expect to see soon a new species of Legionella called Legionella kiwii*' (unpublished correspondence). From a CAP perspective the presence of legionellosis was later augmented through collaborative prospective studies by those working in areas of respiratory illness. As a result, it was recognized across the country that more attention should be given to determining the aetiology of CAP cases that were not responding to conventional treatment so that a more accurate picture of LD in New Zealand could be obtained.

Although the aetiologic agent responsible for LD was discovered in 1977, LD cannot be confined to the history books. In fact, globally it has made a resurgence in recent years due to the increase in the number of infections from *Legionella* spp. and case fatality rates remaining high since the organisms' initial discovery. Hence, *Legionella* is now recognized as a 're-emerging' pathogen [111]. The experience of LD during the 1980s and early 1990s – medical, underlying social relations and political processes – anticipated all the multiple factors that underlie the One Health paradigm. Such a paradigm, while by no means a recent invention, was the means for reinvigorating what were to become essential links between human, and environmental health that are now recognized as being so central to LD surveillance and control in New Zealand and globally. But new challenges are emerging for the future. The recent call by the Intergovernmental Panel on Climate Change for LD to be added to the list of important climate-sensitive health issues [112] is a stark reminder of the role that environmental reservoirs including climatic factors play in LD epidemiology and public health therefore reinforcing the continued need for a global One Health approach. The fact that to this day New Zealand continues to maintain a centralized Legionella Reference Laboratory that has responded to a distinctive epidemiological pattern since 1979 [91] is testimony to Bettelheim and Chereshsky whose pioneering work on legionellosis in collaboration with international agencies and other New Zealand health professionals, was so instrumental to the diagnostic testing and surveillance history that has been built up in New Zealand. Such a legacy is worthy of recognition for its inspiration well beyond their generation.

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None.

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