Original Article
Seroepidemiology of legionellosis in mainland China

Luxi Jiang[1], Shuang Zheng[2,3], Yu Chen[1], Xiaoming Zhou[1], Jiangwei Ma[2], Jian Kang[2], Li Zhao[1]

[1]Department of Respiratory Medicine, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China; [2]Department of Respiratory Medicine, The First Affiliated Hospital of China, Medical University, Shenyang, Liaoning, China; [3]Department of Respiratory Medicine, Central Hospital Affiliated to Shenyang Medical College, Shenyang, Liaoning, China

Abstract: A comprehensive and current understanding of prevalent species and serogroups of Legionella is essential for disease detection. Through a meta-analysis of articles published from January 1982 to December 2014, we investigated the prevalence of species and serogroups of *Legionella* in mainland China. The study included 71 articles on legionellosis patients and 13 on asymptomatic seropositive persons. The predominant *Legionella pneumophila* serogroups were serogroup 1 (sg1), sg6 in patients and sg12, sg4, sg6 in asymptomatic seropositive persons. Besides, there was a statistically significant difference in the distribution of *Legionella* serogroups for both the patients and the asymptomatic seropositive persons between southern and northern China. Our results indicate that *L. pneumophila* is still the most common species in mainland China as other countries with its unique epidemiological characteristics. These data highlight the need for attention to seroepidemiological features and the choice of appropriate diagnostic methods in order to avoid missed diagnosis.

Keywords: Legionella, seroepidemiology, serogroup, mainland China

Introduction

Legionella, the causative agent of Legionnaires' disease, was first discovered by investigators at the United States Centers for Disease Control and Prevention in 1977, following a common-source outbreak of pneumonia among members attending an American Legion convention in Philadelphia in July, 1976 [1, 2]. It has since been identified as a significant aetiological agent of community-acquired pneumonia (CAP), responsible for both sporadic cases and outbreaks ranging in size from small to large worldwide. To date, *Legionella* infections account for 2-15% of worldwide CAP cases, while in mainland China the rate is 5.1% [3-6]. More than 50 species of *Legionella* and 70 serogroups (sg) have been identified [7]. Among them, *Legionella pneumophila* (*L. pneumophila*) is the most common species, leading to approximately 90% of all Legionnaires' disease cases. Although there are now at least 16 serogroups of *L. pneumophila*, approximately 85% of all Legionnaires' disease cases are caused by *L. pneumophila* serogroup 1 (sg1), according to an international collaborative survey [3, 8, 9].

However, the seroepidemiology of legionellosis differs with geographical location and the features of different *Legionella spp*. Recent surveys indicate that *L. pneumophila* sg1 accounts for 70 to 92% of laboratory-detected legionellosis cases in the United States and Europe, but only 50% of the cases in Australia [10]. In Australia and New Zealand, *L. longbeachae* is responsible for 30 to 55% of *Legionella* infection cases [10]. The different seroepidemiology of *Legionella* serogroups in different countries is closely associated with the detection methods used.

At present, detection methods mainly include: culture, urinary antigen test, serological investigation, direct fluorescent-antibody (DFA), and polymerase chain reaction (PCR). Culture in selective media is considered to be the 'gold standard method' because of its ability to detect all strains of the bacterium, but it requires a prolonged incubation period, and sputum cultures are often negative. The urinary antigen test is considered to be sensitive only for *L. pneumophila* sg1. Nevertheless, it is widely accepted as a routine diagnostic method
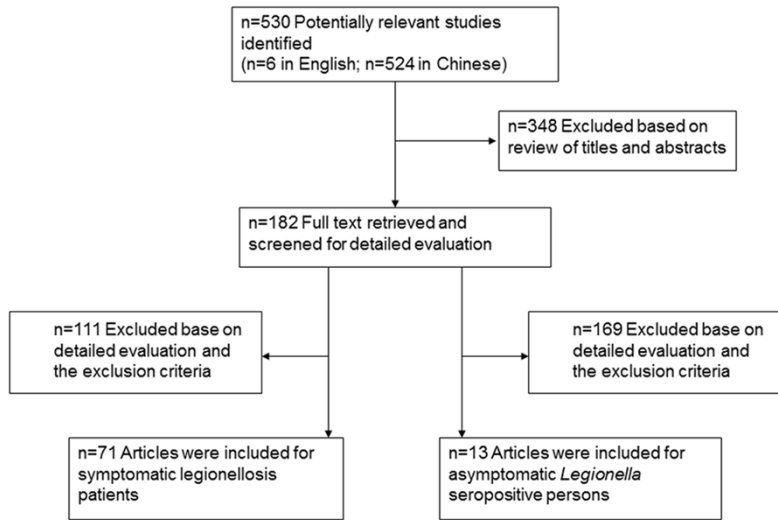
Figure 1. Flow chart of systematic literature search.

Legionella disease was first reported in 1982 in mainland China [18]. So far, there is no epidemiological data on legionellosis from national surveys, which makes the appropriate detection method in mainland China unclear. In this study, we performed a systematic review of published data on *Legionella* species and serogroups circulating in mainland China during 1982-2014, in order to guide the clinical use of detection methods.

Methods

Data sources and search strategy

We systematically searched the PubMed, Chinese Biomedical Literature Database on Disc, China National Knowledge Infrastructure, Wanfang Data Periodicals System, and VIP Chinese Biomedical Journals databases for articles published between January 1982 and December 2014. Various combinations of the terms "legionellosis", "*Legionella*", "Legionnaire", "Legionnaires disease", "legionnaires' disease", "epidemic", "epidemiologic", "epidemiological", "epidemiology", "serum", "serology", "serotype", "type", "serogroup", and "seroprevalence" were used to identify potentially relevant studies.

Inclusion and exclusion criteria for publications

Publications addressing the prevalent species and serogroups of *Legionella* in mainland China during January 1982 to December 2014 were considered relevant.

Review articles, congress abstracts, guidelines, data from regions outside China, articles that repeated or contained data significantly overlapping with those of another published report, studies containing discrepant data, and articles without an available full text version were excluded. Articles failing to mention any serogroups from *L. pneumophila* sg1 to *L. pneumophila* sg14 were also excluded, as were articles failing to report precise isolate numbers of the different species and serogroups of *Legionella*.

for its speed, uncomplicated procedure, and ease of sample collection, accounting for 82% and 97% of cases diagnosed in Europe and the United States, respectively [11-15]. Serological investigation is the main method for detecting non-*L. pneumophila* species and non-sg1 strains, which is valuable for retrospective epidemiological investigations. DFA staining is a rapid method of directly detecting *Legionella spp.* in respiratory secretions and tissue samples. Although rapid, problems with both sensitivity and specificity have limited the use of DFA staining in most laboratories. PCR has the potential to detect infections caused by all of the known species of *Legionella* within a short time [3]. It is meaningful for early diagnosis, especially for urinary antigen-negative and culture-negative cases. However, sometimes it is difficult to obtain respiratory samples, and this hampers PCR detection. As each method has its advantages and disadvantages, it is important to choose reasonable detection methods in different countries, relying on their own epidemiological characteristics. For example, in countries such as the United States and Europe, the urinary antigen test is preferred, while in countries such as Australia, New Zealand, and Scotland, serology or PCR might be used as a primary diagnostic test [16]. The mortality rate of hospitalized patients with CAP caused by *Legionella* is 5-30%. Half of all *Legionella*-based CAP patients need to be treated in the intensive care unit (ICU) [17]. Therefore, early diagnosis with appropriate detection methods and effective treatment is vital for suspected patients.

Table 1. The geographical distribution of *Legionella* serogroups for symptomatic patients with *Legionella* disease in mainland china, 1982-2014

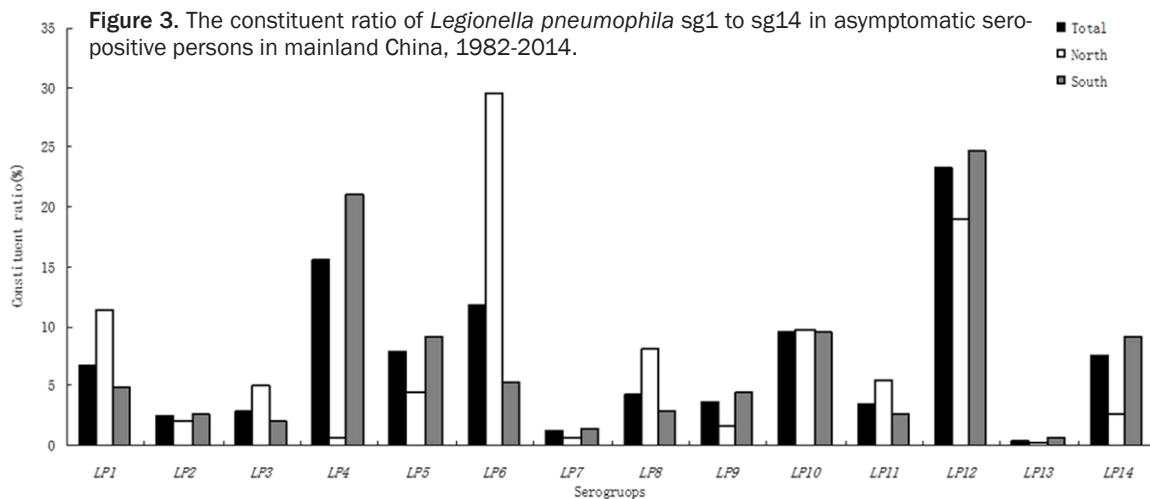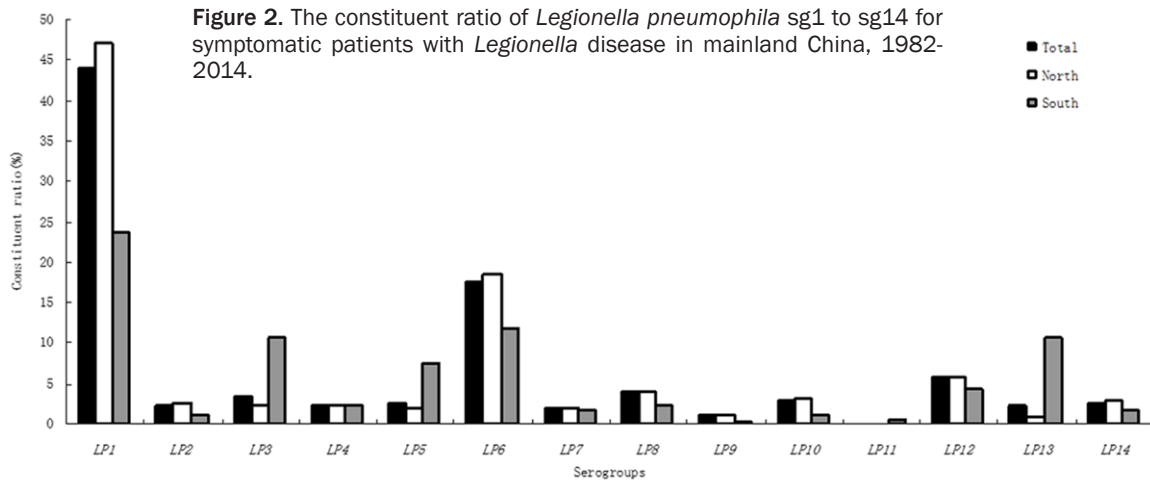| Geographic area	No. of studies	No. of total person	Serogroups																			
			LP1	LP2	LP3	LP4	LP5	LP6	LP7	LP8	LP9	LP10	LP11	LP12	LP13	LP14	Lm	Ll	Lb	Lj	Ld	Mixed type
Total	71	2086	914	48	71	46	56	369	40	82	24	59	2	119	49	55	47	5	21	1	16	62
Total constituent ratio for all the serogroups (%)			43.82	2.30	3.40	2.21	2.68	17.69	1.92	3.93	1.15	2.83	0.10	5.70	2.35	2.64	2.25	0.24	1.01	0.05	0.77	2.97
Northern Chinese	53	1794	845	45	40	39	34	334	35	75	23	56	0	106	18	50	14	4	20	1	0	55
Northern Chinese constituent ratio for all the serogroups (%)			47.10	2.51	2.23	2.17	1.90	18.62	1.95	4.18	1.28	3.12	0.00	5.91	1.00	2.79	0.78	0.22	1.11	0.06	0.00	3.07
Southern Chinese	18	292	69	3	31	7	22	35	5	7	1	3	2	13	31	5	33	1	1	0	16	7
Southern Chinese constituent ratio for all the serogroups (%)			23.63	1.03	10.62	2.40	7.53	11.99	1.71	2.40	0.34	1.03	0.68	4.45	10.62	1.71	11.30	0.34	0.34	0.00	5.48	2.40

LP: Legionella Pneumophila; Lb: Legionella bozemanae; Lm: Legionella micdadei; Ll: Legionella longbeachae; Lj: Legionella jordanis; Ld: Legionella dumoffii.

Table 2. The geographical distribution of *Legionella* serogroups for asymptomatic seropositive persons in mainland china, 1982-2014

Geographic area	No. of studies	No. of total person	No. of positive person	Positive rate (%)	Serogroups														
					LP1	LP2	LP3	LP4	LP5	LP6	LP7	LP8	LP9	LP10	LP11	LP12	LP13	LP14	Lm*
Total	13	6765	2228	32.93	293	111	126	692	350	525	51	188	162	424	149	1032	21	330	12
Total positive rate (%)					4.33	1.64	1.86	10.23	5.17	7.76	0.75	2.78	2.39	6.27	2.20	15.25	0.31	4.48	0.18*
Total constituent ratio for serogroup 1-14 (%)					6.58	2.49	2.83	15.54	7.86	11.79	1.15	4.22	3.64	9.52	3.35	23.17	0.47	7.41	
Northern Chinese	6	4116	1124	27.31	133	23	60	6	52	350	7	96	18	116	64	225	2	30	2
Northern Chinese positive rate (%)	-	-			3.23	0.56	1.46	0.15	1.26	8.50	0.17	2.33	0.44	2.82	1.55	5.47	0.05	0.73	0.05*
Northern Chinese constituent ratio for serogroup 1-14 (%)					11.25	1.95	5.08	0.51	4.40	29.61	0.59	8.12	1.52	9.81	5.41	19.00	0.17	2.54	
Southern Chinese	7	2649	1104	41.68	160	88	66	686	298	175	44	92	144	308	85	807	19	300	10
Southern Chinese positive rate (%)	-	-			6.04	3.32	2.49	25.90	11.25	6.61	1.66	3.47	5.44	11.63	3.21	30.46	0.72	11.33	0.38*
Southern Chinese constituent ratio for serogroup 1-14 (%)					4.89	2.69	2.02	20.97	9.11	5.35	1.34	2.81	4.40	9.41	2.60	24.66	0.58	9.17	

LP: Legionella Pneumophila; Lm: Legionella micdadei. Lm*: Only two article tested *Lm* in Northern China. Only three article tested *Lm* in Southern China.

Figure 2. The constituent ratio of *Legionella pneumophila* sg1 to sg14 for symptomatic patients with *Legionella* disease in mainland China, 1982-2014.

Figure 3. The constituent ratio of *Legionella pneumophila* sg1 to sg14 in asymptomatic seropositive persons in mainland China, 1982-2014.

The inclusion criteria for patients with *Legionella* disease was that the patients meet the diagnostic criteria and that precise information on species and serogroups of *Legionella* was available in the articles. The diagnostic criteria for *Legionella* disease include symptoms of pneumonia, radiological signs of infiltration, and laboratory evidence of infection with *Legionella spp.* Laboratory evidence included one or more of the following criteria: (1) Culture of any *Legionella spp.* from respiratory tissues, respiratory secretions or blood. (2) Fourfold or greater rise in a convalescent serum or more than 256 antibody titer in acute phase of single serum when using indirect immunofluorescent antibody test (IFA) to any *Legionella* serogroup or species. (3) Detection of *L. pneumophila* antigen in urine. (4) Fourfold or greater rise in a convalescent serum or more than 320 antibody titer in acute phase of single serum when using

microagglutination test or enzyme-linked immunosorbent assay (ELISA) to any *Legionella* serogroup or species. Suspected cases which were not confirmed and articles without exact serogroups of *Legionella* were excluded.

The definition of asymptomatic seropositive persons was individuals showing positive antibodies against *Legionella* without clinical symptoms. This could, however, indicate individuals infected with *Legionella* in the past, either with mild symptoms or asymptomatically.

Data extraction

The data were extracted independently by two reviewers (LX. Jiang and Y. Chen) and were rechecked after the first extraction. Any disagreement regarding eligibility during the extraction was discussed by the two reviewers

and resolved. We gathered the following information from original publications: first author, year of publication, study duration, population of the study investigated, province of the study investigated, and experimental methods for identifying serogroups and individual number of patients with each serogroup.

Study profiles

Data on the *Legionella* serogroups for the patients with symptomatic *Legionella* disease, and for asymptomatic *Legionella* seropositive persons, was summarized. According to each subject's region of residence, all cases were classified as either northern Chinese or southern Chinese, with the Qinling-Huaihe Line serving as the geographical boundary.

Statistical analysis

Data were assessed using the Pearson x^2 test (SPSS version 17.0). When any expected number in the 2×2 contingency table was less than 5 and greater than or equal to 1, the *p* value was calculated using a continuity correction test. A value of *P* < 0.01 was considered statistically significant.

Results

Description of the selected articles

We identified a total of 530 articles by a systematic literature search using different combinations of key terms from several databases. After screening titles and abstracts, 348 non-relevant articles were excluded. The 182 remaining articles were retrieved in full text. Of these, 111 were further excluded according to the exclusion criteria. Finally, 71 articles on legionellosis patients were included. Of the 182 full-text retrieved articles, 13 were included on asymptomatic seropositive persons. The selection procedure for this study is illustrated in a flow diagram (**Figure 1**).

Seroepidemiology of legionellosis patients

The geographical distribution of *Legionella* serogroups for the patients with *Legionella* disease is shown in **Table 1** and **Figure 2**. Data on 2,086 cases of Legionnaires' disease were collected. More studies and cases were performed in northern China than in southern China. On the whole, sg1 and sg6 were found to be the two predominant species, with constituent ratios of 43.82% and 17.69%, respectively. Sg12 (5.70%) ranked next, behind them. The other serogroups only represented a small proportion each, ranging from 0.05% to 3.93%. There were few reports on non-*pneumophila Legionella* species infections, *L. micdadei* being the predominant one among these, accounting for 2.25% of all serogroups.

Sg1 and sg6 are the two predominant species among sg1 to sg14 in both the southern China and northern China. However, significant differences in the distribution of serogroups were observed in southern and northern China for patients with *Legionella* disease (P=0.000, P < 0.001). The distribution of serogroups in northern China was quite similar to the whole. However, the distribution of serogroups in southern China was quite different, and more broadly diverse. Although sg1 still ranked in the first place in southern China, the proportion of it was only 23.63%, much lower than that in northern China. Sg6, sg3, sg5, and sg13 were equally distributed and each accounted for 7%-12% of the total disease.

Seroepidemiology for asymptomatic Legionella seropositive persons

The geographical distribution of *Legionella* serogroups for the asymptomatic seropositive persons is shown in **Table 2** and **Figure 3**. A total of 6,765 people were enrolled, while the number of asymptomatic *Legionella* seropositive persons was 2,228 (32.93%) (**Table 2**). In northern China, 1,124 (27.31%) of 4,116 people had positive laboratory results, compared with 1,104 (41.68%) of 2,649 people in southern China (**Table 2**). The positive rate (41.68%) in southern China was higher than that in northern China (27.31%). Comparison of these two positive rates was carried out by x^2 tests with the level for statistical significance set at P < 0.001 (x^2=150.639, P=0.000).

On the whole, sg12, sg4, and sg6 were found to be the three predominant species, with summarized constituent ratios of 23.17%, 15.54%, and 11.79%, respectively. In northern China, sg6, sg12, and sg1 are the top three serogroups, with constituent ratios of 29.61%, 19.00%, and 11.25%; the other remaining serogroups each accounted for less than 10%. Whereas in southern China, the top serogroups

were sg12 (24.66%) and sg4 (20.97%), the other remaining serogroups still accounted for less than 10%. There was also a statistically significant difference in distribution of *Legionella* serogroups for the asymptomatic seropositive persons between the two groups from different regions (x^2=945.471, P=0.000, P < 0.001).

There were far fewer studies on non-*pneumophila Legionella* species for asymptomatic seropositive persons. In our study, only five articles mentioned *L. micdadei* with a rate of 0.18%.

Discussion

In the present study, we reported the prevalence of species and serogroups of *Legionella* in mainland China, in both legionellosis patients and asymptomatic seropositive persons. Although there were few reports on non-*pneumophila Legionella* species, from the current data, *L. pneumophila* is still the most common species in mainland China, as in other countries. In legionellosis patients in mainland China, *L. pneumophila* sg1 ranked first, with a constituent ratio of 43.82%. Compared with Europe and the United States (70 to 92%), the proportion of sg1 in mainland China is low. Even though the prevalence of sg1 in China was similar to that in Australia, there were still differences. In Australia, *L. longbeachae* is remarkably more prevalent than in other countries, due to contaminated potting mixes or composts [10]. Unlike in other countries, sg6 represented a considerable proportion (17.69%) of the serogroups in mainland China. For comparison, sg6 only represented 12 (2%) of 720 culture-confirmed cases in Europe [19]. These results indicate that *Legionella* infection in China exhibits unique epidemiological characteristics. Even between northern China and southern China, distribution differences existed. The distribution of serogroups for patients with *Legionella* disease in northern China was quite similar to that of China as a whole. However, the distribution of serogroups in southern China was quite different, showing a much broader distribution.

Two studies reported on the prevalence of *Legionella* disease among CAP cases in mainland China. One, a multicentre study on the pathogenic agents in 665 adult patients with CAP in seven cities of China, indicated that *L.*

pneumophila were identified in 31/610 patients (5.1%) by paired sera antibody detection [6]. The other survey, which explored the etiologic characteristics of adult patients with CAP in Beijing, showed that *Legionella* was detected in 3/500 (0.6%) cases by urinary antigen test (Binax Now kit) [20]. Neither of these studies reported specific *Legionella* serogroups. The reason for the different *Legionella*-positive rates may be as follows: the urinary antigen test is specific only for *L. pneumophila* sg1, whereas serological investigation can detect all serogroups of *L. pneumophila*. The different data between the two surveys indicates that non-*pneumophila* sg1 serogroups might represent a considerable proportion of total *Legionella* disease in mainland China. This is consistent with our results, and is a reminder of the importance of using various detection methods instead of the urinary antigen test alone in China, in order to avoid missed diagnosis, especially in southern China.

An analysis by Danish researchers has revealed an alarming trend: mortality rates for all non-sg1 legionellosis patient groups were higher than those for any sg1-infected population [21]. Similarly, high levels of mortality were observed in the United States between 1980 and 1989 for patients infected with *L. pneumophila* sg6 [22]. Moreover, the reported survival rate is low (73%) for cases who are culture-positive but urinary antigen test negative [12], a pattern which is more likely for non-sg1 infections. The possible reasons for the higher mortality rate in these subgroups include (1) the wide use of the urinary antigen test, and (2) virulence diversity between serogroups. The urinary antigen test leads to earlier diagnosis and treatment for patients with sg1. In contrast, methods for the detection of non-sg1 serogroups are limited, which may lead to delayed diagnosis and poor prognosis. The second possible reason is that different serogroups could differ in their virulence, and non-sg1 *Legionella* may be more pathogenic. The prevalent species and serogroups of *Legionella* in mainland China are different from those in other countries, especially with regard to sg6, which occupied a higher proportion of symptomatic *Legionella* infections in China compared with other countries. On the basis of these data, the mortality rate of legionellosis in mainland China may be higher than in other areas in the world, and this needs to be further studied.

The positive rate for the asymptomatic *Legionella* seropositive persons in southern China was statistically higher than that in northern China, which indicates that the prevalence of asymptomatic infection might be higher in southern China. As we know, *Legionella spp.* are ubiquitous in freshwater habitats, including rivers, lakes, streams, ponds and man-made water systems, such as air-conditioning cooling towers, whirlpool spas, and fountains. The bacteria thrive in tepid water (25°C to 37°C). Compared with the northern China, the climate in southern China is warmer and more humid. The southern China is also more economically developed, with more natural and artificial water systems. These factors may also be related to the high rate of asymptomatic *Legionella* seropositive persons.

There was also a statistically significant difference in the distribution of *Legionella* serogroups among asymptomatic *Legionella* seropositive persons between the northern China and the southern China. Sg6, sg12, and sg1 were the top three serogroups in northern China, while the top serogroups were represented by sg12 and sg4 in southern China.

The data showed that sg12 accounted for 23.17% of asymptomatic seropositive persons, vs. only 5.70% of patients with symptomatic *Legionella* infection. Also, the prevalence of sg4 in asymptomatic seropositive persons and symptomatic patients was 15.54% and 2.21%, respectively. This implies that different serogroups may have different virulence. It also indicates that the virulence of sg12 and sg4 may be relatively weak, probably leading to subclinical infection rather than pneumonia, but the mechanism of this needs to be further studied.

Several limitations of this review should be noted. The fact that not all studies offered information about non-*pneumophila* species makes it difficult to draw accurate conclusions about the prevalence of non-*pneumophila* serogroups. This is a retrospective study, and the articles involved were published in different periodicals; this may lead to publication bias. In addition, the fact that the detection methods varied among different articles may also give rise to some bias. To achieve a precise estimate, further large-scale population-based surveillance studies using standardized methods are required.

To our knowledge, this is the first study to systematically review the seroepidemiology of *Legionella* in mainland China over the past several decades. Our results reveal significant differences in serogroups between China and other countries. Although sg1 still ranked first, as in other countries, the rate of sg1 in China is relatively low. Also, unlike in other countries, sg6 occupied a considerable proportion among the serogroups in symptomatic legionellosis patients. Finally, China is vast in territory, and the distribution of serogroups of *Legionella* varied between northern China and southern China. This study highlights the importance of attention to seroepidemiological features in suspected legionellosis patients, particularly with regard to appropriate diagnostic methods in order to avoid missed diagnosis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yu Chen, Department of Respiratory Medicine, Shengjing Hospital of China Medical University, No 36 Sanhao Street, Heping District, Shenyang 110004, China. Tel: 86-24-96615-21111; Fax: 86-24-23845961; E-mail: chenyusy@hotmail.com

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