# COVID-19 Co-infection with *Legionella pneumophila* in 2 Tertiary-Care Hospitals, Germany

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We describe screening results for detection of co-infections with *Legionella pneumophila* in patients infected with severe acute respiratory syndrome coronavirus 2. In total, 93 patients were tested; 1 was positive (1.1%) for *L. pneumophila* serogroup 1. Co-infections with *L. pneumophila* occur in coronavirus disease patients and should not be missed.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease (COVID-19), is characterized by severe respiratory distress, fever, and cough. High death rates, especially in older persons and those with underlying health conditions, have been described (*1*). According to World Health Organization guidelines and public health agencies, persons with cardiovascular disease, chronic respiratory disease, diabetes, and cancer are considered to be at increased risk for severe COVID-19. Moreover, the risk of becoming severely ill increases with age ≥60 years (https://www.who.int/publications/m/item/covid-19-and-ncds).

Groups at risk are largely the same for COVID-19 and Legionnaires' disease (LD), a severe and potentially fatal pneumonia caused by *Legionella* spp. These bacteria are found in many environments, including complex building water systems. In Europe and North America, *Legionella* spp. account for ≈1%–16% of all community-acquired pneumonias that require hospitalization (*2*); in 2017, the overall notification rate was 1.8/100,000 population for the European Union/European Economic Area (European Centre for Disease Prevention and Control, https://www.ecdc.europa.eu/en/publications-data/legionnaires-disease-annual-epidemiological-report-2017). *L. pneumophila* is responsible for >90% of LD cases; specifically, serogroup 1 causes 70%–80% of LD cases in the United States and Europe (*3*). Currently, the Centers for Disease Control and Prevention and the European Society of Clinical Microbiology and Infectious Diseases Study Group for Legionella Infections give warning of increased risk for *Legionella* spp. infections resulting from stagnant or standing water in plumbing systems after the temporary shutdown of buildings and reductions in normal water use (*4*,*5*). A single person with SARS-CoV-2 revealed *L. pneumophila* co-infection in the context of travel (*6*). This case underlines the importance of making differential diagnoses during the COVID-19 pandemic by diagnostic microbiology to identify other infectious microorganisms causing similar symptoms.

In this retrospective analysis, we evaluated the co-occurrence of infections with *L. pneumophila* in patients infected with SARS-CoV-2. We performed urine antigen tests for detection of *L. pneumophila* serogroup 1 (BinaxNOW Legionella; Abbott Rapid Diagnostics Germany GmbH, https://www.de.abbott). We analyzed urine samples from 93 patients from 2 tertiary-care hospitals in Germany: University Hospital Essen, Essen, and General Hospital Nürnberg, Nuremberg. This retrospective study was approved by the Ethics Committee of the Medical Faculty at the University of Duisburg-Essen, Germany (approval no. 20–9335-BO).

The cohort was mostly male (71.0%) and had a mean age of 65 years; 90% had symptoms of pneumonia (Table). All were hospitalized, and 38.7% received mechanical ventilation. More than one third of the cohort had ≥2 underlying conditions and reflected the groups at risk for infection with *Legionella* spp.

We detected 1 *L. pneumophila* serogroup 1 antigen in the entire cohort (1.1%). The patient with *L. pneumophila* serogroup 1 co-infection was a 41-year-old man with severe acute respiratory deficiency syndrome and bronchial asthma as underlying disease; he initially came to the hospital with fever, cough, and dyspnea and had no recent travel history. Before admission to the University Hospital, he was treated with azithromycin and ceftriaxone for 4 days, until a switch to levofloxacin on day 1 after first diagnosis of LD in the referral hospital. In the University Hospital, urine antigen test was still positive, and detection of *Legionella* spp. DNA from bronchoalveolar fluid revealed a PCR cycle threshold value of 34 (ampliCube Respiratory Panel 1; Mikrogen Diagnostic, https://www.mikrogen.de), which was assessed as negative. To exclude a false-positive antigen test result, we retested this specific urine sample after boiling for 5 min and centrifugation (5 min at 12,000 × *g*), which yielded a positive result again (*7*). As of July 2020, the patient was still critically ill, receiving mechanical ventilation and intravenous levofloxacin (500 mg 2×/d; day 6 of levofloxacin treatment).

**Table.** Demographics and underlying conditions of patients with COVID-19 examined for *Legionella pneumophila* urine antigen, Germany

| Characteristic | Value |
|---|---|
| Total | 93 (100.0) |
|    Negative for *L. pneumophila* serogroup 1 antigen | 92 (98.9) |
|    Positive for *L. pneumophila* serogroup 1 antigen | 1 (1.1) |
| Average time between admission and *Legionella* antigen test processing | 2.6 d (mean), 1 d (median) |
| Legionella-specific culture† performed/positive | 18 (19.4)/0 |
| Legionella nonspecific culture performed/positive | 35 (37.6)/11 (31.4) |
| Multiplex PCR‡ performed/positive | 31 (33.3)/5 (16.1) |
| Clinical symptoms typical for COVID-19§ | 60 (90.0) |
| Hospitalized | 93 (100) |
|    Transferred from other hospital | 35 (37.6) |
|    Treated in intensive care unit | 40 (43.0) |
| Mean age, years | 65 |
| Sex | |
|    M | 66 (71.0) |
|    F | 27 (29.0) |
| Invasive mechanical ventilation | 36 (38.7) |
| Extracorporeal membrane oxygenation | 17 (18.3) |
| Mortality | 30 (32.3) |
| Underlying conditions | |
|    Cardiovascular disease | 50 (53.8) |
|    Diabetes | 28 (30.1) |
|    Chronic respiratory disease | 13 (14.0) |
|    Cancer | 10 (11.0) |
|    Other: rheumatism, Parkinson's disease | 17 (18.3) |
|    Addictions: alcohol, nicotine | 7 (7.5) |
|    Solid organ transplantation: lung | 1 (1.1) |
|    None | 15 (16.1) |
|    1 underlying condition | 55 (59.1) |
|    2 underlying conditions | 29 (31.2) |
|    >2 underlying conditions | 7 (7.5) |

*Values are no. (%) except as indicated.
†Legionella BMPA selective agar (Thermo Scientific, https://www.thermofisher.com).
‡Unyvero P50 pneumonia application (Curetis GmbH, https://curetis.com) or ampliCube Respiratory Panel 1 (Mikrogen Diagnostic, https://www.mikrogen.de).
§Data available for 67 patients.

Xing et al. reported *L. pneumophila*, detected by indirect immunofluorescence in 20% of COVID-19 patients, as the second most prevalent bacterium causing respiratory disease (Q. Xing et al., unpub. data, https://www.medrxiv.org/content/10.1101/2020.02.29.20027698v2). However, cross-reactivity of indirect immunofluorescence tests with other bacterial species has been described. Antibody titers without follow-up should be interpreted with caution because antibodies can be generated even after mild infections and can persist over years.

In view of epidemiologic data, detection of only *L. pneumophila* serogroup 1 antigen in urine is a suitable diagnostic approach for outpatient-acquired and travel-associated pneumonia, with varying sensitivity and specificity (8). The false-negative rate of this diagnostic approach is low because antigen excretion starts 24 hours after first symptoms and generally persists for weeks, and in rare cases even months (9); positive urine antigen tests can be found after initiation of antimicrobial drug treatment. However, pretest probability of *L. pneumophila* pneumonia should be reasonably high to have clinical utility (10).

The findings from our small cohort study in 2 geographically distinct areas in Germany indicate that co-infections with *L. pneumophila* serogroup 1 can occur in patients with COVID-19. Clinicians treating patients positive for SARS-CoV-2 should be aware of possible co-infections with *L. pneumophila* and should use appropriate diagnostic approaches.

## About the Author

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# Temporal Variations in Respiratory Syncytial Virus Epidemics, by Virus Subtype, 4 Countries

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Temporal variation of respiratory syncytial virus (RSV) epidemics was recently reported to be determined by the dominant RSV subtype. However, when we repeated the analysis for 4 countries in the Northern and Southern Hemispheres, the dominant subtype did not seem to affect temporal variation of RSV epidemics.

Respiratory syncytial virus (RSV) is responsible for most acute lower respiratory tract infections in young children worldwide (*1*) and accounts for a substantial burden among older adults (*2*). Although it is generally accepted that RSV epidemics in temperate climates occur in winter, some temporal variation epidemics remains unexplained (*3*).

Recently, Yu et al. conducted a study among children (<13 years of age) with pneumonia at the Beijing Children's Hospital (Beijing, China) during July 2007–June 2015 and reported that temporal variation is partly explained by seasonal differences in virus subtype dominance (*4*). To define the timing of RSV seasonality, they used a regression model and 10% threshold method previously described (*3*). They found that onset and peak of seasons occurred ≈3–5 weeks earlier and that duration was ≈6 weeks longer when RSV subtype A (RSV-A) was dominant than when subtype B (RSV-B) was dominant. These results, if generalizable, would have major implications for the