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Long-term impacts of Legionnaires' disease on health and wellbeing: rationale, study design and baseline findings of a matched cohort study (LongLEGIO)

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Summary

BACKGROUND AND STUDY AIMS: Is there a post-acute infection syndrome for Legionnaires' disease? Legionnaires' disease is a form of primarily community-acquired pneumonia caused by *Legionella* spp. bacteria. Legionnaires' disease and other forms of bacterial community-acquired pneumonia may lead to persistent health and wellbeing impairments. It remains unclear whether these are caused by the community-acquired pneumonia-causing pathogen or the pneumonia itself. We present the rationale and design of a matched cohort study to investigate the persistent health impacts of Legionnaires' disease and compare them with persistent manifestations of other bacterial (Legionella test-negative) community-acquired pneumonia. We also present baseline characteristics of the study cohorts.

METHODS: Legionnaires' disease patients and Legionella test-negative community-acquired pneumonia patients with confirmed or clinically suspected bacterial aetiology were recruited from university and cantonal/regional hospitals and matched for sex, age, hospital type and date of diagnosis. Questionnaire-based interviews are conducted at baseline and 2, 6 and 12 months after the start of appropriate antibiotics. The questionnaires focus on patient-reported outcome measures and cover long-term symptoms, use of health services and health-related quality of life.

RESULTS: Between June 2023 and June 2024, 59 patients with Legionnaires' disease (59.3% male, median age 69 years [interquartile range [IQR]: 57–80]) and 60 patients with other bacterial (Legionella test-negative) community-acquired pneumonia (63.3% male, median age 69 years [IQR: 60–79]) were enrolled. Admission to the intensive care unit was required for 13.6 % of Legionnaires' disease patients and 8.3 % of other bacterial community-acquired pneumonia patients. Chronic kidney failure was more prevalent among Legionnaires' disease patients (15.3% vs 10.0%), while chronic obstructive pulmonary disease (20.0% vs 11.9%), malignancies (33.3% vs 13.6%) and an immunocompromised status (25.0% vs 13.6%) were more common in Legionella test-negative community-acquired pneumonia patients. Furthermore, Legionella test-negative community-acquired pneumonia patients reported lower baseline quality of life scores than Legionnaires' disease patients. Differences in pneumonia severity, comorbidities and self-reported quality of life scores will be accounted for in future analyses.

CONCLUSIONS: The LongLEGIO study will contribute to research on post-acute infection syndromes and provide the data for a more holistic assessment of the disease burden of Legionnaires' disease.

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Introduction

Lower respiratory tract infections, including pneumonia, remain a major cause of morbidity and mortality worldwide [1, 2] and pose a significant burden on healthcare systems [3]. Symptoms of pneumonia and overall impaired wellbeing can persist for weeks to months after the acute infection, leading to additional use of health services [4–6]. Persistent sequelae of pneumonia that are reported in the literature include respiratory symptoms such as cough, dyspnoea and chest discomfort [7], cardiovascular complications [8], cognitive impairment [9, 10], general fatigue [7, 11, 12] and reduced quality of life [13]. Notably, extrapulmonary sequelae often outlast the respiratory symptoms [6, 11]. In addition, up to 9% of patients experience recurrent pneumonia within five years of an acute pneumonia episode [14].

Persistent manifestations of pneumonia – particularly non-specific symptoms such as fatigue or cognitive impairment and general reduced wellbeing – are difficult to capture in clinical practice and are often not well documented in medical records [7, 15, 16]. As a result, patient-reported outcome measures (PROMs) collected in prospective studies are important endpoints for assessing recovery from pneumonia [7]. However, most such prospective pneumonia studies do not differentiate between pneumonia-causing pathogens in the analysis but instead stratify for *Streptococcus pneumoniae* as the most commonly identified cause of community-acquired pneumonia (CAP) [11, 17] or they report persistent symptoms for individual pathogens without comparing findings to pneumonia of other aetiologies [18, 19]. The role of the infecting organism in the persistence of pneumonia symptoms therefore remains poorly understood.

Studying and comparing persistent symptoms of Legionnaires' disease (LD) with other bacterial pneumonia provides an opportunity to investigate the role of the infection-causing pathogen in persistent pneumonia sequelae. Legionnaires' disease is caused by the intracellular Gram-negative Legionella bacterium and accounts for about 4–7% of CAP cases in Europe [20]. Legionnaires' disease often causes severe pneumonia and, in addition to respiratory symptoms, is frequently associated with extrapulmonary manifestations such as confusion, diarrhoea, headache and acute kidney damage [21–23]. The underlying pathophysiological mechanisms of Legionella infections are very similar to those of *Coxiella burnetii* infections causing Q fever [24, 25]. The long-term health effects of Q fever, particularly chronic fatigue, are well documented in the literature [15].

Despite its potential to cause persistent symptoms and health impairments that might be even more pronounced than for other types of bacterial pneumonia, the chronic impact of Legionnaires' disease remains little studied. Previous studies have reported persistent fatigue, neurological symptoms such as concentration difficulties and memory loss, muscle weakness and reduced quality of life for up to 17 months after an acute Legionella infection [18, 26]. However, the studies were not specifically designed to compare these symptoms with the persistent manifestations of other types of pneumonia. It therefore remains unclear whether the observed persistent sequelae were due to the underlying Legionella infection or more generally due to the severity of the pneumonia per se. In addition, no study has systematically assessed the use of health services by Legionnaires' disease patients beyond the acute phase of infection.

Here, we describe the rationale and design of the LongLEGIO study. This prospective study explores the persisting impacts of community-acquired Legionnaires' disease (CALD) on patients' health, wellbeing and health service utilisation and compares CALD patients with bacterial community-acquired pneumonia patients who tested negative for Legionella. We will further present the baseline characteristics of the two study cohorts.

Methods

Study design and objectives

The LongLEGIO study is a matched cohort study with the following objectives: (a) To explore CALD patients' persistent symptoms and general wellbeing and compare them to those of Legionella test-negative bacterial community-acquired pneumonia patients (non-LD CAP), and (b) To describe and compare the care needs and health service utilisation of CALD and non-LD CAP patients during their recovery.

Recruitment and data collection

The LongLEGIO study enrolled CALD and non-LD CAP patients from university and cantonal/regional hospitals in Switzerland. For the recruitment of CALD patients and the collection of baseline data on these patients, the LongLEGIO study builds on a national case-control and molecular source attribution study investigating risk factors and sources of infection for CALD in Switzerland (*SwissLEGIO*) (figure 1) [27].

Recruitment of community-acquired Legionnaires' disease patients

CALD patients were recruited from a representative pool of Legionnaires' disease patients who participated in the *SwissLEGIO* study [27]. The *SwissLEGIO* study recruited 204 CALD patients between August 2021 and March 2024 from 20 university and cantonal hospitals across Switzerland, which jointly reported about 45% of all CALD cases notified to the Swiss health authorities during this period [27]. CALD patients, who previously participated in the *SwissLEGIO* study, were eligible to participate in the LongLEGIO study if they fulfilled the study criteria summarised in table 1. CALD patients were invited to participate in the LongLEGIO study by post or e-mail. Written informed consent was obtained from all CALD patients prior to the two-month follow-up interview (figure 1).

Recruitment of Legionella test-negative bacterial community-acquired pneumonia patients

Non-LD CAP patients were recruited through one university and three cantonal hospitals. All four hospitals also participated in the *SwissLEGIO* parent study. During the recruitment period, the hospitals kept track of all community-acquired pneumonia patients with pneumonia of confirmed or clinically suspected bacterial aetiology and who tested negative for *Legionella* spp. and COVID-19. The recruitment of the non-LD CAP patients occurred as soon as possible after the patients were diagnosed with pneumonia (figure 1).

To ensure comparability, non-LD CAP patients were matched to CALD patients based on sex, age (±5 years), hospital level (university or cantonal hospital) and date of diagnosis (up to +60 days). The recruitment of the non-LD CAP patients was triggered by the enrolment of a CALD patient – eligible for the LongLEGIO study – into the *SwissLEGIO* parent study. In short, a recruitment request with the match criteria was sent to the four partner hospitals. The eligible non-LD CAP patient with the closest matching diagnosis date was recruited. Eligibility criteria

for non-LD CAP patients are summarised in table 1. Written informed consent was obtained prior to the baseline interview.

Data collection

For the LongLEGIO study, the two cohorts of CALD patients and non-LD CAP patients are followed up over 12 months. Assessments are done at four different time points (figure 1). As soon as possible after the pneumonia di-

Figure 1: Recruitment, enrolment and data collection for the community-acquired Legionnaires' disease (CALD) and Legionella test-negative bacterial community-acquired pneumonia (non-LD CAP) cohorts. Grey: Baseline interviews and data extraction from electronic medical records for CALD patients were done within the context of the *SwissLEGIO* parent study. Red: LongLEGIO recruitment and data collection for the CALD cohort. Patients were recruited two months after the acute infection from a pool of CALD patients previously included in the *SwissLEGIO* parent study. Yellow: LongLEGIO recruitment and data collection for the non-LD CAP cohort. Non-LD CAP patients were enrolled from four university and cantonal/regional hospitals shortly after the pneumonia diagnosis. ABT: appropriate antibiotic therapy; CAP: community-acquired pneumonia; LD: Legionnaires' disease.

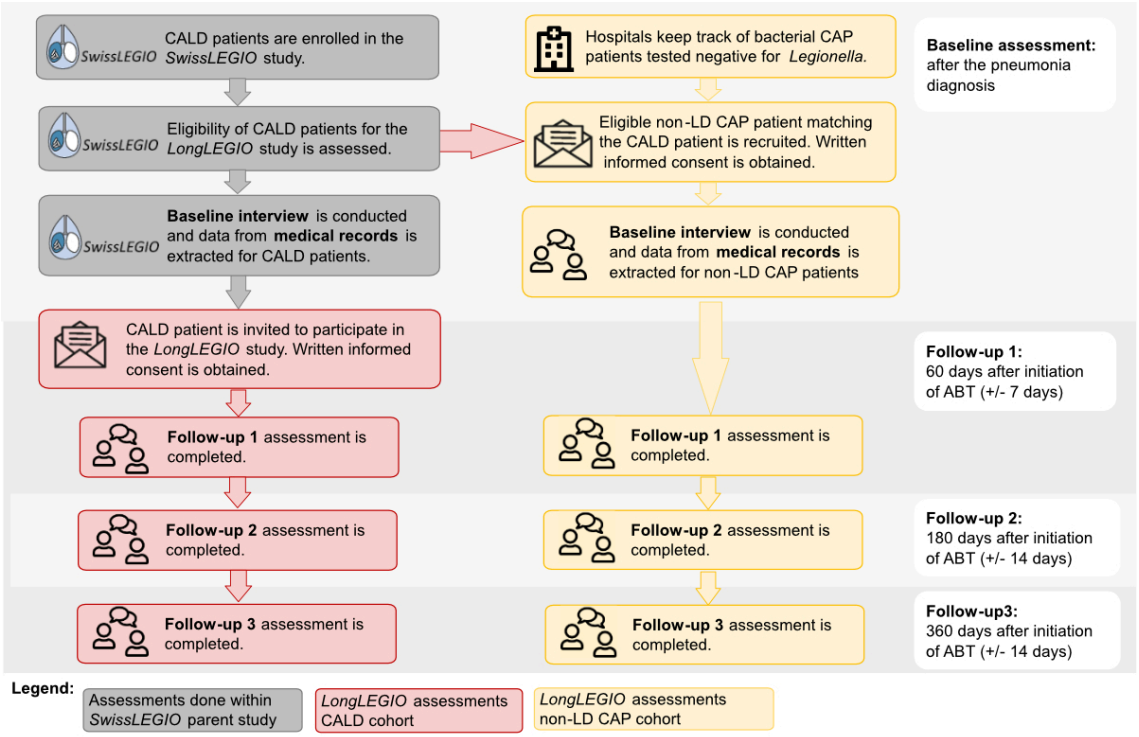

Table 1:
Eligibility criteria for participation in the LongLEGIO study for community-acquired Legionnaires' disease patients and Legionella test-negative bacterial community-acquired pneumonia patients.

	Inclusion criteria	Exclusion criteria
Community-acquired Legionnaires' disease	Lives in Switzerland and speaks German, French, Italian or English	Suspected hospital-acquired pneumonia
	Aged ≥18 years	Suspected travel-associated pneumonia
	Health status permits provision of informed consent and participation in the study	No COVID-19 laboratory test was performed**
	Clinical signs and symptoms are suggestive of Legionnaires' disease (confirmed pneumonia*)	Laboratory-confirmed COVID-19 infection at hospital admission
	Laboratory-confirmed *Legionella* spp. infection (urinary antigen test, PCR or culture on sputum/ tracheobronchial aspirates)**	
Non-Legionnaires' disease community-acquired pneumonia	Lives in Switzerland and speaks German, French, Italian or English	Suspected hospital-acquired pneumonia
	Aged ≥18 years	Suspected travel-associated pneumonia
	Health status permits provision of informed consent and participation in the study	No COVID-19 laboratory test was performed**
	Confirmed pneumonia*	Laboratory-confirmed COVID-19 infection at hospital admission
	Confirmed or suspected bacterial origin of pneumonia***	
	Laboratory test for *Legionella* spp. (urinary antigen test, PCR or culture on sputum/ tracheobronchial aspirates) performed and negative**	

* Confirmed pneumonia was defined as the presence of a new infiltrate (chest X-ray, ultrasound or CT scan) PLUS clinical symptoms suggestive of pneumonia (fever, chills, cough, sputum, dyspnoea, tachypnoea, thoracic pain).

** Legionella urinary antigen test, Legionella-specific PCR or Legionella-specific culture and the COVID-19 laboratory test were done as part of the routine diagnostics and clinical case management of the patient at the hospital level.

*** Pneumonia must be classified as "bacterial" or "suspected bacterial" in the medical records and be treated with a full course of antibiotics for at least 3 days [28]. A viral pneumonia with bacterial superinfection was included when treated with a full course of antibiotics.

agnosis, a questionnaire-based baseline interview is conducted and additional data are extracted from electronic medical records for the current hospitalisation. Follow-up assessments are conducted at 2, 6 and 12 months after patients have received appropriate antibiotic therapy. All interviews are conducted in person or by a phone/video call.

At baseline, the questionnaire consists of closed and open questions related to patients' pre-existing comorbidities, their acute illness experience, the perceived disease severity and patients' health-seeking (table 2). In addition to the baseline interview, information on the patient's medical history, disease severity, the pneumonia-causing pathogen and the treatment was extracted from electronic medical records.

The follow-up questionnaire focuses on patient-reported outcome measures used in previous studies assessing recovery from pneumonia [7, 13, 33–35] and in studies on Long COVID [36–38]. The questionnaire consists of closed and open questions to investigate (a) the patient's perceived health, recovery and health-related quality of life (HRQoL) after the acute pneumonia episode, (b) the presence of persistent pneumonia-related symptoms, (c) patients' (potentially extended) health service utilisation and health-seeking in the informal health sector after hospital discharge, and (d) potential impacts of the infection on patients' social and work life (table 2).

Statistical analysis

Considering sample size, we assumed a 15% prevalence of symptoms such as fatigue, weakness and a general reduction in quality of life in the non-LD CAP group two months after the acute pneumonia episode. We therefore aimed to recruit and complete the first follow-up interview for 80 CALD patients and 80 non-LD CAP patients to detect a 20% difference between our two cohorts with 80% power and alpha = 0.05. The achieved sample size (59 CALD patients and 60 non-LD CAP patients) is sufficient to provide a power of 70% with alpha = 0.05.

The statistical analyses are being conducted according to the predefined Statistical Analysis Plan (SAP), available in the appendix**.** In summary, CALD and non-LD CAP patients were characterised at baseline in terms of demographics, illness experience, help-seeking, comorbidities and health-related quality of life. Continuous variables are presented as medians with interquartile ranges (IQRs) and categorical variables as n (%).

To assess long-term effects, we will tabulate the prevalence of symptoms and impairments in the EQ-5D-5L dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as n (%). EQ-VAS scores will be reported as medians with IQRs at baseline (0 months), 2, 6 and 12 months. We will use bar charts and histograms to present the distribution of symptoms and health-related quality of life measures over time and to visualise differences between cohorts.

To estimate differences in the perceived overall recovery and in the recovery of selected symptoms between CALD and non-LD CAP, we will use non-parametric survival models. Differences in time to recovery between groups will be compared using log-rank tests with survival curves visualised using Kaplan-Meier estimates. Confounders such as selected comorbidities and working status will be accounted for using inverse probability weighting (IPW). Changes in health-related quality of life measures are estimated using a linear or logistic mixed model with a random effect on the individual patient. We will again correct for confounders.

Healthcare utilisation – including visits to general practitioners, specialist physicians, emergency departments and rehospitalisations – will be analysed across the entire follow-up period and within each follow-up interval. We will assess both the proportion of patients consulting healthcare services at least once for any reason and the proportion of patients consulting healthcare services specifically due to

Table 2:
Content of the LongLEGIO questionnaire.

Baseline questionnaire	
Patient characteristics	Demographic information (e.g. sex, age, education, income)
Illness experience and health-seeking for acute pneumonia	Pneumonia manifestation
	Disease perception and perceived severity of the pneumonia
	Health-seeking prior to hospital admission
Comorbidities and health-related quality of life	Comorbidities
	Health-related quality of life prior to pneumonia (EQ-5D-5L) [29]
Follow-up questionnaire	
Perceived recovery from pneumonia and health-related quality of life	Subjective judgement on overall health
	Subjective assessment of the degree of recovery from pneumonia
	5-item World Health Organisation Well-being Index (WHO-5) [30]
	Health-related quality of life at the time of follow-up interview (EQ-5D-5L) [29]
Persistent symptoms	Presence and perceived severity of symptoms (extensive list of pneumonia symptoms reported in the literature is provided). Patients are asked to judge whether symptoms are related to the pneumonia.
	Quantification of dyspnoea (modified Medical Research Council [mMCR]) [31]
	Fatigue assessment scale (FAS) [32]
	Worsening of pre-existing comorbidities or newly diagnosed medical conditions
Healthcare utilisation and patients' health-seeking behaviour	Quantification of formal healthcare utilisation since the last assessment
	Quantification of health-seeking outside the formal health sector since the last assessment
	Changes in prescribed / newly prescribed medications
	Patient experiences in navigating the health system and perceived challenges
Social life and work participation	If persisting symptoms: impact on work participation and social life

pneumonia after hospital discharge. Additionally, we will report the absolute number of consultations.

Only participants who completed at least the first follow-up interview will be included in the analysis. Missing data will be imputed using logical rules. No further imputation for missing values is foreseen.

All analyses will be conducted using R (version 4.4.1; R Core Team, Vienna, Austria).

Data management

Data are collected on standardised electronic Case Report Forms (eCRF) using the data collection software Open Data Kit (ODK, getodk.org). Forms are encrypted and all patient-identifying information is removed. Individual forms are linked through unique subject identification. Automated validations are implemented in the eCRF to check for data completeness and plausibility and submitted forms are continuously checked for plausibility and accuracy. Data are stored on a secured network drive accessible only to authorised study personnel.

Ethical considerations

Ethical approval for the study was obtained from the Ethics Commission of Northwestern and Central Switzerland (EKNZ 2023-00639) and the boards of the participating hospitals. This study is conducted in accordance with the principles of Good Epidemiological Practice and the Declaration of Helsinki. Data are stored in concordance with Swiss data protection laws.

Study population

Enrolment

The recruitment timelines and the sample size for the LongLEGIO study were bound to the enrolment of CALD patients in the *SwissLEGIO* parent study. Overall, 86 CALD patients and 110 non-LD CAP patients were invited to participate in the LongLEGIO study between June 2023 and June 2024. In total, 59 CALD patients (enrolment rate of 69%) and 60 non-LD CAP patients (enrolment rate of 55%) agreed to participate. There were no significant differences in age, sex and ICU admission rates between participants and non-participants among CALD patients, and in sex and ICU admission rates among the patients with non-LD CAP (appendix table S1). There was a difference in age between participants and non-participants among the non-LD CAP patients (69 years vs 77 years).

Baseline characteristics

The baseline characteristics are summarised in table 3. The median age for both cohorts is 69 years; males comprised 59.3% of CALD and 63.3% of non-LD CAP patients. Both cohorts have a similar comorbidity burden as measured by the Charlson Comorbidity Index. Non-LD CAP patients, however, were more likely to have chronic obstructive pulmonary disease (COPD) (20.0% vs 11.9%), malignancies (33.3% vs 13.6%) and were more likely immunocompromised (25.0% vs 13.6%). In contrast, more CALD than non-LD CAP patients had chronic kidney failure (15.3% vs 10.0%). Patients in both cohorts exhibited similar health-seeking behaviour prior to the hospital visit with the majority of patients initially consulting a general practitioner. CALD patients were more frequently pretreated with antibiotics (30.4% vs 15.3%).

During the acute phase of their pneumonia, non-LD CAP patients more frequently reported respiratory symptoms including cough (80.0% vs 66.7%), shortness of breath (78.0% vs 66.1%) and chest pain (49.1% vs 35.1%). On the contrary, CALD patients reported more frequent extrapulmonary symptoms such as fever (89.3% vs 76.3%), muscle aches (51.8% vs 25.9%), headaches (47.3% vs 28.1%), and nausea or emesis (11.9% vs 3.3%). The ICU admission rate and the proportion of patients who needed invasive ventilation were higher for CALD than for non-LD CAP patients (13.6% vs 8.3% and 6.8% vs 1.8%, respectively).

Finally, participants were asked to report on their perceived health-related quality of life prior to the onset of pneumonia symptoms. We used the standardised EQ-5D-5L questionnaire which measures health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In addition, patients are also asked to rate their overall health on a scale from 0 (lowest possible score) to 100 (EQ-VAS score) [29]. In general, non-LD CAP patients reported lower EQ-VAS scores compared to CALD patients. Differences in the reported health-related quality of life were observed for the dimensions mobility, daily activity and pain/discomfort (table 3, appendix table S2).

For non-LD CAP patients, *Streptococcus pneumoniae* and *Haemophilus influenzae* were each identified as the causative pathogen in 10.0% of the patients. *Mycoplasma pneumoniae* was the causative pathogen in 5.0% of patients. Viral-bacterial pneumonia with bacterial superinfection was recorded for 3.3% of non-LD CAP patients. No pathogen was detected in 73.3% of non-LD CAP patients (appendix table S2).

Discussion

Acute infections can cause persistent health problems. Although post-acute infection syndromes have been recognised for some time, they have often been neglected and underreported, with few exceptions like Q fever [15]. The COVID-19 pandemic, however, brought renewed attention to this issue, when long-term health and wellbeing impairments were observed in a significant subset of patients months or even years after the acute SARS-CoV-2 infection [36–38]. Similarly, persistent health impairments have been reported for community-acquired pneumonia [8–13, 17]. However, the role of the infection-causing pathogen in the persistence of community-acquired pneumonia symptoms and sequelae in general remains unclear, and data on the long-term health effects of Legionnaires' disease are scarce. Here, we described the rationale and design of a matched cohort study to investigate persistent sequelae of community-acquired Legionnaires' disease (CALD) and compare them with manifestations of persistent pneumonia in non-LD CAP patients. We also presented the baseline characteristics of our two study cohorts, which are representative of their respective patient populations.

Previous studies on persistent sequelae of community-acquired pneumonia have rarely stratified analyses by the

Table 3:
Baseline characteristics of 119 Legionnaires' disease patients and non-Legionnaires' disease bacterial community-acquired pneumonia patients.

			Community-acquired Legionnaires' disease (n = 59)	Non-Legionnaires' disease community-acquired pneumonia (n = 60)
Patient characteristics	Male		35 (59.3%)	38 (63.3%)
	Age, median [IQR]		69 [57–80]	69 [60–79]
	Annual household income	<60,000 CHF	15 (36.6%)	21 (39.6%)
		60,000–100,000 CHF	21 (51.2%)	22 (41.5%)
		>100,000 CHF	5 (12.2%)	10 (18.9%)
	Body mass index in kg/m^2, median [IQR]		24.0 [22.0–28.0]	25.0 [21.0–28.0]
Medical conditions	Comorbidities*	Heart disease	21 (35.6%)	25 (41.7%)
		Heart failure	7 (11.9%)	8 (13.3%)
		Diabetes mellitus	7 (11.9%)	10 (16.7%)
		Chronic obstructive pulmonary disease	7 (11.9%)	12 (20.0%)
		Chronic kidney failure	9 (15.3%)	6 (10.0%)
		Cerebrovascular disease	5 (8.5%)	6 (10.0%)
		Malignancy (haematological/solid organ)	8 (13.6%)	20 (33.3%)
		Immunosuppression**	8 (13.6%)	15 (25.0%)
	Charlson Comorbidity Index, median [IQR]		1 [0–2]	2 [0–3]
	Active smokers (self-reported)		20 (33.9%)	13 (22.4%)
Health-seeking prior to hospital visit	Medical advice prior to admission	None	20 (34.5%)	18 (30.5%)
		General practitioner	28 (48.3%)	26 (44.1%)
		Hospital/emergency department	2 (3.4%)	6 (10.2%)
		Specialist doctor	4 (6.9%)	5 (8.5%)
		Caregiver/family members/close friends	7 (12.1%)	6 (10.2%)
	Antibiotics prescribed prior to current pneumonia/ hospital admission	None	39 (66.1%)	50 (83.3%)
		Amoxicillin/clavulanic acid	15 (25.4%)	6 (10.0%)
		Cephalosporin	1 (1.7%)	0 (0.0%)
		Combination therapies***	1 (1.7%)	1 (1.7%)
		Prior antibiotic treatment with unknown agent	0 (0.0%)	2 (3.3%)
		Unknown if prior antibiotics	3 (5.1%)	1 (1.7%)
	Time from symptom onset to hospital admission in days, median [IQR]		4 [2–6]	5 [3–10]
Self-reported symptoms during the acute phase of illness	Fatigue/weakness		55 (94.8%)	49 (83.1%)
	Fever		50 (89.3%)	45 (76.3%)
	Cough		38 (66.7%)	48 (80.0%)
	Shortness of breath		37 (66.1%)	46 (78.0%)
	Muscle aches		29 (51.8%)	15 (25.9%)
	Headache		26 (47.3%)	16 (28.1%)
	Chest pain		20 (35.1%)	28 (49.1%)
	Confusion		19 (33.3%)	20 (35.1%)
	Diarrhoea		15 (26.3%)	17 (28.8%)
	Nausea/emesis		7 (11.9%)	2 (3.3%)
	Loss of appetite		5 (8.5%)	4 (6.7%)
	Self-rated severity#, median [IQR]		8 [7–9]	7 [5–8]
Progression of pneumonia and severity	Time from hospital admission to start of adequate antibiotic treatment in days, median [IQR]		0 [0–1]	0 [0–0]
	Length of hospital stay in days, median [IQR]		6 [4–9]	6 [4–7]
	Intensive care unit admission		8 (13.6%)	5 (8.3%)
	Non-invasive ventilation		7 (11.9%)	12 (28.6%)
	Invasive ventilation		4 (6.8%)	1 (1.8%)
	Discharge followed by	Outpatient care	47 (81.0%)	52 (86.7%)
		Referral to another hospital	5 (8.6%)	0 (0.0%)
		Referral to a rehabilitation centre	6 (10.3%)	8 (13.3%)
Quality of life (EQ-5D-5L)##	Mobility		14 (23.7%)	22 (36.7%)
	Self-care		2 (3.4%)	3 (5.0%)
	Usual activities		13 (22.0%)	20 (33.3%)
	Pain/discomfort		20 (34.5%)	26 (43.3%)
	Anxiety/depression		20 (35.1%)	20 (33.3%)
	EQ-VAS score, median [IQR]		85 [75–90]	70 [50–85]

* As reported in the electronic medical records; ** Treatment with steroids (≥7.5 mg prednisolone-equivalent/day for more than 4 weeks), cytostatic or immunosuppressive drugs OR HIV infection with CD4 <200/µl OR neutropenia OR history of a haematological stem cell transplantation OR asplenia OR a primary immunodeficiency; *** Amoxicillin/clavulanic acid or cefepime in combination with macrolides

Likert scale from 1 to 10

We present any impairments in the five dimensions of health, regardless of reported severity

different pneumonia-causing pathogens [8–10, 12, 13]. Of those that have, the focus has been on *Streptococcus pneumoniae* [11, 17]. This limited stratification was mainly due to sample size limitations and a lack of information on the community-acquired pneumonia-causing pathogens. In contrast, studies examining persistent sequelae of Legionella infections did not include pneumonia patients as a comparison group [18, 26]. To our knowledge, the LongLEGIO study is the first study that systematically compares the persistent health effects of CALD with the persistent manifestations of non-LD CAP, going beyond a survival analysis based on mortality data [39]. Such a comparison is crucial to contextualise the frequency of observed health and wellbeing impairments in CALD patients against the background occurrence in a suitable control group. Moreover, this approach will allow us to explore how the persistence of community-acquired pneumonia-related health impairments is linked to the pathogenic mechanisms of the causative bacteria. Ultimately, this may improve our understanding of the underlying pathogenesis of persistent pneumonia manifestations and post-acute infection syndromes [15, 16].

The LongLEGIO study prioritised patient-reported outcome measures, rather than focusing on mortality or hospital readmission rates which have been the primary outcomes in previous large studies on Legionella that relied on medical record data [39, 40]. Such patient-reported outcome measures provide robust measures of persistent symptoms and functional impairments that patients experience [7]. Persistent symptoms and functional impairments, as measured by patient-reported outcome measures, are also one of the main reasons for additional general practitioner consultations and emergency department visits after the acute phase of pneumonia [4, 5]. Patient-reported outcome measures, however, are usually not well documented in medical records and hence can only be adequately captured by applying prospective study designs [15, 16].

The LongLEGIO study is also the first study to assess healthcare utilisation among CALD patients beyond the acute infection and its association with persistent sequelae of CALD. As demonstrated by the COVID-19 pandemic and the rise of Long COVID, post-acute infection syndromes can significantly contribute to the burden of infectious diseases [16, 37]. However, current estimates of the burden of Legionnaires' disease do not account for persistent health impairment or the resulting increased medical costs [41, 42]. By examining both persistent sequelae of CALD and additional healthcare utilisation after the acute infection, the LongLEGIO study will provide data for a better disease burden estimate for Legionnaires' disease in the future. This, in turn, may help public health specialists and physicians to plan and anticipate the health care resources needed for the holistic treatment of CALD beyond the acute phase of the disease.

A total of 59 CALD patients and 60 non-LD CAP patients were enrolled between June 2023 and June 2024. Our non-LD CAP and CALD patient cohorts appear representative of the two patient populations. Similarly to what is reported in previous studies, Legionnaires' disease patients were more likely to suffer from extrapulmonary symptoms, were more frequently pre-treated with antibiotics before hospital admission and were more often admitted to the ICU [21–23, 43]. Non-LD CAP patients, on the other hand, were more likely to suffer from chronic obstructive pulmonary disease, immunosuppression and malignancies, which is also consistent with findings from previous research [23, 43]. Finally, we also observed differences in the self-reported quality of life scores (lower scores were reported by non-LD CAP patients). Both comorbidities and pneumonia severity may influence the long-term health outcomes after pneumonia [4, 6, 11]. We will therefore correct for these differences in our future analyses of long-term outcomes. For the self-reported quality of life score, each patient will serve as their control and relative rather than absolute changes in reported scores from the pre-pneumonia baseline score will be assessed and compared between groups.

The LongLEGIO study has limitations. First, the study may be subject to recall bias, especially between the 6- and 12-month follow-up points. We try to mitigate this recall bias by specifically probing for both intermittent and current symptoms. In addition, interviewers are instructed to systematically probe for all the symptoms and health service consultations that were reported by the patient in previous interviews. Second, despite the integration of the LongLEGIO study into the national *SwissLEGIO* parent study, our sample size for CALD remains relatively small. It is therefore possible that we underestimate functional impairments that are relatively rare although we are confident of fully capturing the common persistent sequelae of CALD. Finally, the study compared only patients surviving hospitalisation, restricting the population of CALD and non-LD CAP.

In summary, the LongLEGIO study explores and compares persistent health and wellbeing impacts of CALD and non-LD CAP in two representative cohorts. The study aims to contribute to ongoing research on post-acute infection syndromes, a phenomenon long recognised and well-documented for conditions like Q fever but often challenging to capture in daily medical practice [15]. Here, we presented the rationale and study design of the LongLEGIO study and characterised the two study cohorts. Results of the long-term follow-up of these two cohorts will be reported in subsequent publications.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *WCA* has received travel grants (Pfizer, Gilead) and reimbursement for advisory boards (Pfizer, MSD, Sanofi-Aventis, GSK, OM Pharma, Janssen, Moderna) or presentations (Pfizer, MSD, GSK, Gilead), paid to his institution. No other potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

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Study summary

The *LongLEGIO* study is a matched cohort study to examine persistent health impacts of community-acquired Legionnaires' disease (CALD) and compare them with persistent manifestations from other bacterial (*Legionella* test-negative) community-acquired pneumonia (non-LD CAP). The two cohorts of CALD and non-LD CAP patients were recruited from cantonal- and university hospitals and matched for sex, age, hospital type and date of diagnosis. Semi-structured interviews were conducted at baseline, two, six and 12 months after the start of appropriate antibiotic therapy for the acute infection. The questionnaires focus on patient-reported outcome measures (PROMs) and cover long-term symptoms, use of health services, health-related quality of life, and social/work impact.

Supplementary tables

Table S1: Baseline characteristics of 86 Legionnaires' disease patients (CALD) and 110 non-LD bacterial CAP patients (non-LD CAP) invited to participate in the LongLEGIO study between June 2023 and June 2024

	Enrolled	**Not enrolled**
CALD patients	**N=59**	**N=27**
Age (median [IQR])	69 [57, 80]	65 [60, 75]
Male	35 (59.3%)	17 (63.0 %)
Hospitalisation	57 (96.6 %)	27 (100.0 %)
ICU admission	8 (13.6 %)	4 (14.8 %)
Non-LD CAP	**N=60**	**N=50**
Age (median [IQR])	69 [60, 79]	77 [67, 82]
Male	22 (36.7 %)	19 (38.0 %)
Hospitalisation	58 (96.7 %)	43 (100.0 %)
ICU admission	5 (8.3 %)	1 (2.4 %)

Table S2: Supplementary baseline characteristics of Legionnaires' disease patients (CALD) and non-LD bacterial CAP patients (non-LD CAP)

		CALD (n=59)	non-LD CAP (n=60)
Quality of Life (EQ-5D-5L)			
Mobility	No problem	45 (76.3 %)	38 (63.3 %)
	Slight problem	5 (8.5 %)	8 (13.3 %)
	Moderate problem	6 (10.2 %)	10 (16.7 %)
	Severe problem	3 (5.1 %)	4 (6.7 %)
	Extreme problems/ unable to do	0 (0.0 %)	0 (0.0 %)
Self-care	No problem	57 (96.6 %)	57 (95.0 %)
	Slight problem	2 (3.4 %)	3 (5.0 %)
	Moderate problem	0 (0.0 %)	0 (0.0 %)
	Severe problem	0 (0.0 %)	0 (0.0 %)
	Extreme problems/ unable to do	0 (0.0 %)	0 (0.0 %)
Usual activities	No problem	46 (78.0 %)	40 (66.7 %)
	Slight problem	7 (11.9 %)	13 (21.7 %)
	Moderate problem	3 (5.1 %)	5 (8.3 %)
	Severe problem	3 (5.1 %)	2 (3.3 %)
	Extreme problems/ unable to do	0 (0.0 %)	0 (0.0 %)
Pain/Discomfort	No problem	37 (64.9 %)	34 (56.7 %)
	Slight problem	13 (22.8 %)	5 (8.3 %)
	Moderate problem	5 (8.8 %)	15 (25.0 %)
	Severe problem	2 (3.5 %)	6 (10.0 %)
	Extreme problems/ unable to do	0 (0.0 %)	0 (0.0 %)
Anxiety/Depression	No problem	37 (64.9 %)	40 (66.7 %)
	Slight problem	13 (22.8 %)	11 (18.3 %)
	Moderate problem	5 (8.8 %)	5 (8.3 %)
	Severe problem	2 (3.5 %)	4 (6.7 %)
	Extreme problems/ unable to do	0 (0.0 %)	0 (0.0 %)
Usual health-seeking prior to infection			
General practitioner		49 (83.1 %)	46 (78.0 %)
Hospital/Emergency department		4 (6.8 %)	4 (6.7 %)
Specialist doctor		5 (8.5 %)	4 (6.7 %)
Care giver/Family members/Close friends		18 (30.5 %)	10 (16.7 %)
Pharmacy		10 (16.9 %)	1 (1.7 %)
Telemedicine		2 (3.4 %)	2 (3.3 %)
Self-reported pre-existing comorbidities			
High blood pressure[1]		22 (37.9 %)	24 (41.4 %)
Ischemic heart disease		7 (11.9 %)	11 (18.3 %)
Heart failure		3 (5.3 %)	7 (12.1 %)
Cerebrovascular disease in the past		4 (6.8 %)	8 (13.8 %)
COPD		6 (10.3 %)	5 (8.6 %)

	CALD (n=59)	non-LD CAP (n=60)
Asthma	8 (13.8 %)	10 (17.5 %)
Pneumonia in the last 5 years	7 (12.1 %)	12 (21.1 %)
Cancer (ongoing + in the last 5 years)	7 (11.9 %)	15 (25.4 %)
Diabetes mellitus	7 (11.9 %)	7 (12.1 %)
Immunosuppression	9 (15.8 %)	14 (26.4 %)
Chronic liver disease	1 (1.7 %)	5 (8.5 %)
Chronic kidney disease	4 (7.0 %)	8 (14.0 %)
Aetiology of non-LD pneumonia		
Unspecified aetiology	-	44 (73.3 %)
Streptococcus pneumoniae	-	5 (8.3 %)
Streptococcus pneumoniae and *Haemophilus influenzae*	-	1 (1.7 %)
Mycoplasma pneumoniae	-	3 (5.0 %)
Haemophilus influenzae	-	3 (5.0 %)
Haemophilus influenzae and Rhinovirus	-	2 (3.3 %)
Staphylococcus aureus and *Klebsiella pneumoniae*	-	1 (1.7 %)
Pseudomonas aeruginosa	-	1 (1.7 %)

[1]Based on clinical evaluation

Statistical analysis plan LongLEGIO

Authors: Melina Bigler, Daniel Mäusezahl, Jan Hattendorf
SAP version number 1.0, 4. February 2025

Introduction

Is there a post-acute infection syndrome for Legionnaires' disease (LD)? LD is a form of primarily community-acquired pneumonia (CAP) caused by *Legionella* spp. bacteria. LD and also other forms of bacterial CAP may lead to persistent health and well-being impairments. It remains unclear whether these are caused by the CAP-causing pathogen or the pneumonia itself.

The *LongLEGIO* study is a prospective study that aims to explore the persisting impacts of community-acquired LD (CALD) on patients' health, well-being, and health service utilisation, and compares CALD patients with bacterial CAP patients who tested negative for *Legionella* spp.

Objectives

Primary objective(s)

- To explore CALD patients' persistent symptoms and general well-being.
- To compare CALD patients' persistent symptoms and general well-being to those of *Legionella* test-negative bacterial CAP patients (non-LD CAP).

Secondary objective(s)

- To explore health service utilisation of CALD and non-LD CAP patients during the recovery.
- Qualitatively explore the disease experience, experiences regarding navigating the health system, and the impact of the infection on work participation and social life on CALD and non-LD CAP patients (feasibility tbd, not included in the SAP)

Design and outcomes

Definition of LD: Legionella status, as determined by the hospital's clinical laboratory standard procedures for Legionella diagnostics.

LD patients and Legionella test-negative CAP patients with confirmed or clinically suspected bacterial aetiology were recruited from university and cantonal/regional hospitals and matched for sex, age, hospital type and date of diagnosis. Interviews are conducted at baseline and two, six and 12 months after the start of appropriate antibiotics. The questionnaires focus on patient-reported outcome measures (PROMs) and cover long-term symptoms, use of health services, and health-related quality of life.

Table 1: *Definition of outcomes*

Outcomes	
Self-perceived recovery assessed by questionnaires (PROMs) 2, 6 and 12 months after diagnosis.	1= not fully recovered, 0= fully recovered
Sequelae symptoms	Sequelae symptoms are defined as newly occurring and persistent, or worse than the status before CAP/CALD, and which cannot be explained by an alternative disease. 0= absent, 1 =present
EQ-5D-5L	→ The five dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression will be dichotomised (0=no problems/ 1=any problems) → for the EQ-VAS scale absolute scores (discrete scale (usually integers from 0 to 100), treated as continuous for the analysis) will be considered
Healthcare re-consultation due to pneumonia (overall, readmission)	Defined as a consultation of a GP, a physiotherapist, or a walk-in clinic, a visit to the emergency department, or a hospital re-admission (individual and pooled) reported for any reason and reported to be due to the pneumonia.

Statistical analysis

Statistical principles

Statistical tests and confidence intervals will be two-sided. Estimates will be presented with 95% confidence intervals. P-values will be presented where appropriate. No adjustments will be made for multiple testing. Interpretations will be based on the strength of evidence of effect size and consistency of results for related outcomes.

The statistical analysis will be conducted using the statistical software R Version 4.4.1 (R Core Team, Vienna, Austria).

Patient characteristics

At baseline, CALD patients and non-LD CAP patients are characterised in terms of demographics, illness experience, help-seeking, comorbidities and HRQoL. Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as n (%).

From the follow-up assessments, we will add the following variables to the table: newly diagnosed medical conditions, re-infections, insurance status, hospital re-admissions, and information on mortality.

Analysis of primary objectives

Exploration of persistent sequelae/ quality of life impact for CALD and non LD-CAP

We tabulate the prevalence of individual symptoms and of HRQoL impairments for the five EQ-5D-5L dimensions (n (%)) and median (IQR) for the absolute EQ-VAS score at 0, 2, 6 and 12 months for CALD and non-LD CAP separately.

We will use bar charts and histograms to visualise findings by study group, e.g. prevalence of symptoms over time, distribution and changes in the EQ-VAS score.

Comparison of CALD patients' persistent symptoms and general well-being to those of Legionella test-negative bacterial CAP patients (non-LD CAP)

We tabulate the prevalence of symptoms (n (%)) and HRQoL measures (n (%) and median (IQR)) for CALD and non-LD CAP at 0, 2, 6 and 12 months. We will again use bar charts and histograms (i.e. for the EQ-VAS score) to visualise differences between the two groups over time.

To estimate differences in perceived overall recovery and in the recovery of selected symptoms from CALD and non-LD CAP, we will use non-parametric survival models. Differences in time to recovery between groups will be compared using log-rank tests. Survival curves will be visualised using Kaplan-Meier survival curves. We will correct for confounders such as selected comorbidities and working status using inverse probability weighting (IPW).

Changes in HRQoL measures are estimated using a linear or logistic mixed model with a random effect on the individual patient. We will again correct for the confounders described above.

Analysis of secondary objective/ exploratory analysis

Exploration of health service utilisation of CALD and non-LD CAP patients during the recovery

We will describe healthcare utilisation (GP or specialist visits, emergency department visits, re-hospitalisation) for both cohorts over the entire follow-up period and at each follow-up interval. We will consider both, the proportion of patients consulting a health care service at least once for any reason and the proportion of patients consulting a health care service at least once due to the pneumonia after hospital discharge. We will also consider the absolute number of consultations.

We will additionally use stacked bar charts to visualise the absolute number of consultations over time (between 0 and 2 months, 2-6 months and 6-12 months) and to compare the two cohorts.

Missing data

Only participants who completed at least the first of the three follow-up interviews will be included in the analysis (full analysis set). Missing data will be imputed using logical rules (non-recovery at later points implies no recovery at all earlier time points). No further imputation for missing values is foreseen. We will compare the baseline demographic characteristics of participants lost to follow-up with those who remain in the study to assess potential imbalances that could introduce bias.