

## R E V I E W

# Impact of lockdown and non-pharmaceutical interventions on the epidemiology of Legionnaires' disease.

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**Abstract.** *Background and aim.* In order to cope with the requirements of COVID-19 pandemic and prevent overwhelming of the healthcare systems, during 2020 social distancing measures were proposed, and generalized lockdown. Aim of our study is to ascertain whether non-pharmaceutical intervention did have any impact on the epidemiology of Legionnaires' disease (LD), a respiratory infectious disease without interhuman spreading. *Methods.* Official national reports from 4 index countries in European Union (i.e. Germany, France, Italy, and Spain) were retrieved. The study included all cases notified during 2020 COVID-19 outbreak, versus the cases referred during the same period in 2019. Subgroup analyses for hospital-associated and travel-associated LD cases, as well as for lethality estimates were performed. *Results.* A sustained drop for incidence rate was confirmed, at EU-level (3.5 per 100,000 vs. 5.3 per 100,000) as well as in the national estimates. The decrease was particularly evident in Italy (RR 0.880, 95%CI 0.839 to 0.905), despite a transient surge in notification rates during the month of June, 2020. Subgroup analyses demonstrated a fall in travel-associated cases (-66.8% at EU level), while hospital-associated cases decreased in absolute number when compared to 2019, but were substantially stable in terms when compared to EU estimates. While Case Fatality Ratio increased in comparison with 2019, no significant trend was similarly identified in comparison to EU estimates. *Conclusions.* Lockdown measures have impacted on the epidemiology of LD in Europe during 2020, but some heterogeneities were identified both across the assessed countries, and the various subgroup. Even though the absolute number of total cases did substantially decrease in 2020 compared to 2019, the effect of non-pharmaceutical interventions was mostly indirect, through a reduced interaction of individuals with environments at potentially high-risk for human infections (e.g. hospitals, accommodation sites, etc.). ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Legionella, Legionnaires' disease, COVID-19, non-pharmaceutical interventions

## Introduction

Following the unprecedented health threat represented by the Coronavirus Disease 2019 (COVID-19), preventive strategies based on non-pharmaceutical interventions (NPI) have been extensively implemented by various European Countries (1–3). NPI have been defined as public health measures actions, apart from getting vaccinated and taking medicine, that people and communities can take to help slow the spread of illnesses that aim to prevent and/or control the

transmission of a targeted pathogen in the community (4,5). Physical distancing and lockdown measures that have been applied during 2020 have improved the control of the SARS-CoV-2 pandemic when no other preventive interventions were available, and have substantially impacted on the transmission of respiratory pathogens (6), but scarce evidence is to date available on Legionnaires' disease (LD) (7–9).

LD, an atypical pneumonia sustained by intracellular Gram-negative pathogens of the gender *Legionella*, has no acknowledged inter-human spreading (10), and

individuals usually become infected through inhalation of aerosols or aspiration of contaminated water from natural and artificial aquatic environments (11–15). As a consequence, while NPI may have little if any effect on the transmission of this pathogen, lockdown measures and the subsequent stay in closed and contaminated environments may potentially increase the risk for susceptible subjects to become infected (16–18).

The aim of this short report will be, therefore, summarize available data from official National Reports, in order to assess whether the ongoing pandemic and the NPI may have impacted on the epidemiology of LD in Europe during 2020.

## Materials and Methods

Available reports on the LD cases from the four most populated countries of EU (i.e. Germany, France, Italy, and Spain; 57.6% of total population of EU by January 1<sup>st</sup>, 2021) for the timeframe 2020 – 2015 were retrieved from the websites of the competent Health Authorities (i.e. Robert Koch Institut, Santé Publique France, Istituto Superiore di Sanità, Instituto de Salud Carlos III for Germany, France, Italy, and Spain, respectively). Estimates at EU levels and data that were conflicting, lacking or unsuitably reported from the National Bulletins (e.g. lack of point estimates, with preferential graphic representation of incidence data) were retrieved from the European Centre for Disease Prevention and Control (ECDC; See Annex 1). According to available estimates, around 70% of new diagnoses of LD in EU are yearly reported by the aforementioned index countries.

All the aforementioned reports are based on the common framework for case definition of LD (15,19–21) that was implemented at EU-level since 2012. Briefly, *confirmed* case of LD is a patient presenting clinical and/or radiological signs of pneumonia, with at least one of three laboratory criteria including: isolation of *Legionella* spp from respiratory secretions or any normally sterile site; detection of Lp1 antigen in UAT; rise in specific antibody level to Lp1 in paired serum samples. A *probable* case is a patient presenting clinical and/or radiological signs of pneumonia associated with a single high level of specific antibodies to Lp1

( $\geq 1:256$ ), or a positive direct immunofluorescence test, or a positive PCR.

The following data were extracted using a standardized assessment form: number of incident cases, incidence rates, number of deaths, share of hospital-associated LD (HALD; i.e. cases occurring in subjects that were hospitalized at any time in the 10 days before the onset of the symptoms), and travel-associated LD (TALD; i.e. cases occurring in subjects linked to tourist recreational facilities and tourist turnout in the 10 days before the onset of the symptoms).

Results of such analyses were systematically reported, summarized, and compared as follows. Initially, the share of total cases and total LD-associated deaths from the index countries over the whole of LD cases in EU were reported in percent values. Subsequently, the share cases of HALD and TALD were reported in percent values of the parent national report. Data were compared to National estimates for 2019, and to EU estimates in 2020 in order to calculate corresponding Risk Ratio (RR) with their 95% Confidence Intervals (95%CI).

All calculations were performed on R 4.0.3 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>) (22) by means of packages *epiR* (v. 2.0.19), *EpiReport* (v 1.0.1), *fmsb* (0.7.0), *msm* (1.6.8).

*Ethical approval.* No ethical approval was needed for this study, as no individual data were identifiable, and only aggregated, openly available official data were analyzed and presented.

## Results

According to the retrieved data, during the timeframe 2015 – 2019, a total of 45,769 cases of LD were diagnosed at EU-Level (range: 6886 in 2015 to 11331 in 2016): collectively, the index countries accounted to 70.3% of all reported cases in the EU, peaking in Italy (n = 11479, 25.1%), followed by France (n = 8086, 16.4%), Spain (n = 6394, 14.0%), and Germany (n = 6149, 13.4%) (Table 1).

During 2020, even though the share of the index countries over the total reports increased to 72.1%, all

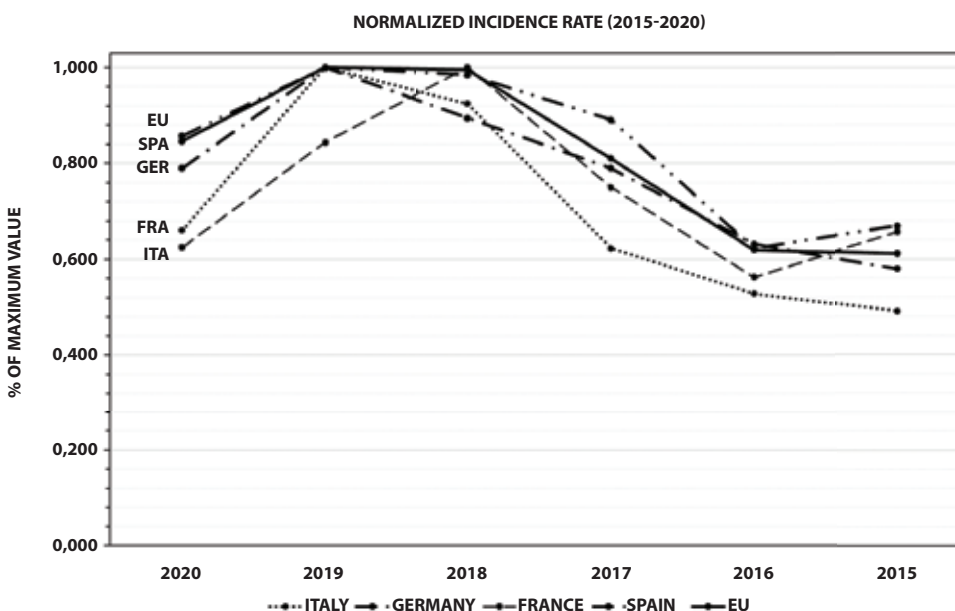
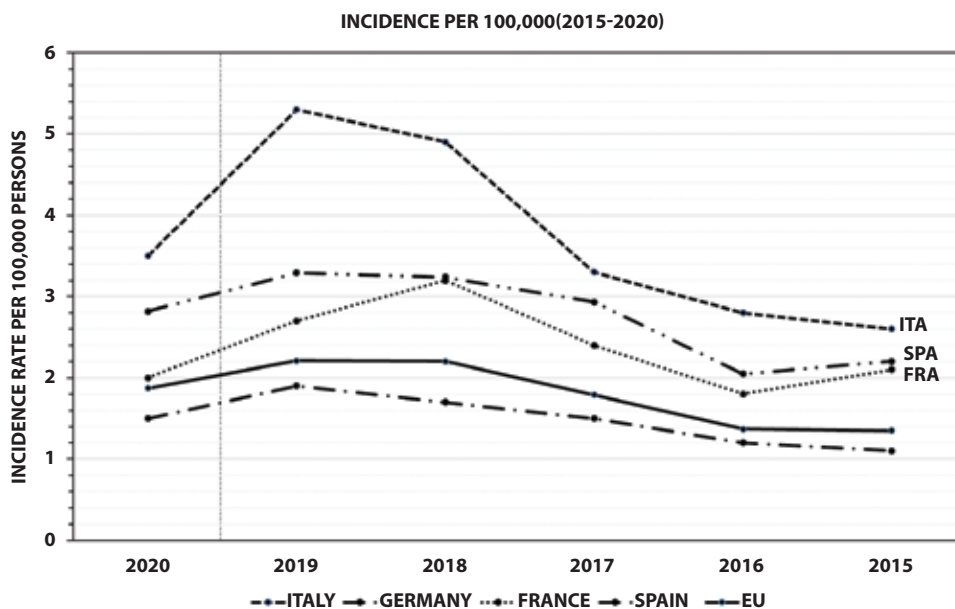
**Table 1.** Occurrence of Legionnaires' disease in European Union (EU), Germany, France, Italy and Spain in 2020, 2019, and in the timeframe 2015-2019. Note: HALD = Hospital-associated Legionnaires' disease; TALD = Travel-associated Legionnaires' disease.

	2020	2019	2015 – 2019
	No., %	No., %	No., %
<b>European Union</b>			
Total	8333, 100%	11307, 100%	45769, 100%
Incidence rate	3.5 / 100,000 persons	5.3 / 100,000 persons	3.8 / 100,000 persons
HALD	425, 5.1%	690, 6.1%	2715, 5.9%
TALD	650, 7.8%	1956, 17.3%	7573, 16.5%
Deaths	550, 6.6%	637, 5.6%	2800, 6.1%
<b>Germany</b>			
Total (No./EU)	1281, 15.3%	1548, 13.7%	6149, 13.5%
Incidence rate	1.5 / 100,000 persons	1.9 / 100,000 persons	1.5 / 100,000 persons
HALD	44, 3.4%	70, 4.5%	226, 3.7%
TALD	126, 9.8%	353, 22.8%	1252, 20.4%
Deaths	61, 4.8%	84, 5.4%	294, 4.8%
<b>France</b>			
Total (No./EU)	1328, 15.9%	1816, 16.1%	8086, 17.7%
Incidence rate	2.0 / 100,000 persons	2.7 / 100,000 persons	2.4 / 100,000 persons
HALD	84, 6.3%	106, 5.8%	527, 6.5%
TALD	179, 13.5%	334, 18.4%	1543, 19.1%
Deaths	120, 9.0%	160, 8.8%	707, 8.7%
<b>Italy</b>			
Total (No./EU)	2074, 24.9%	3199, 28.3%	11479, 25.1%
Incidence rate	3.5 / 100,000 persons	5.3 / 100,000 persons	3.8 / 100,000 persons
HALD	68, 3.3%	121, 3.8%	510, 4.4%
TALD	133, 6.4%	293, 9.2%	1207, 10.5%
Deaths	99, 4.8%	135, 4.2%	528, 4.6%
<b>Spain</b>			
Total (No./EU)	1336, 16.0%	1542, 13.6%	6393, 14.0%
Incidence rate	2.8 / 100,000 persons	3.3 / 100,000 persons	2.7 / 100,000 persons
HALD	37, 2.8%	74, 4.8%	267, 4.2%
TALD	29, 2.2%	119, 7.7%	443, 6.9%
Deaths	76, 5.7%	82, 5.3%	363, 5.7%

reports seemingly show a decrease in both reported cases and notification rates over the previous reporting year.

Corresponding notification rates ranged between 2.21 per 100,000 in 2019 and 1.35 per 100,000 in 2015. At national levels, incidence rates ranged between 1.1 per 100,000 (2015) and 1.9 per 100,000 (2019) for

Germany, 1.8 per 100,000 (2016) and 3.2 per 100,000 (2018) for France, 2.6 per 100,000 (2015) and 5.3 per 100,000 (2019) for Italy (Figure 1a). When incidence rates were normalized by the maximum one, the peak years were identified in the biennium 2018-2019 at EU level, in 2019 in Italy and Germany, 2018 in France (Figure 1b).



**Figure 1.** Incidence rate for Legionnaires' disease in EU, Italy, Germany, France (2015 – 2020), reported as incident cases per 100,000 people per year (a), and as normalized percent values by the maximum rate during the timeframe (2015-2020) (b).

As shown in Table 2, a substantial decrease in reported cases occurred in 2020 compared to 2019 both at EU-level (i.e. -26.3%; RR 0.736, 95%CI 0.715 to 0.757), and at national level.

However, when the national rates were compared to the EU estimates, the difference in reported cases for Italy (i.e. -35.2%, RR 0.880, 95%CI 0.839 to 0.905) was proportionally greater than that reported

**Table 2.** Occurrence of Legionnaires' disease (LD) in 2020 vs. 2019 estimates. Note: RR = relative risk, 95%CI = 95% Confidence Intervals; HALD = hospital-associated LD; TALD = travel-associated LD; EU = European Union.

	TOTAL CASES		Diff. (%)	HALD		Diff. (%)	TALD		Diff. (%)	Deaths	
	Diff. (%)	RR (95%CI)		RR (95%CI)	RR (95%CI)		RR (95%CI)	RR (95%CI)			
<b>EU</b>	-26.3%	0.736 (0.715; 0.757)	-38.4%	0.836 (0.743; 0.940)	-66.8%	0.451 (0.414; 0.490)	-13.7%	1.172 (1.049; 1.308)			
<b>Germany</b>	-17.2%	0.827 (0.767; 0.890)	-37.1%	0.760 (0.525; 1.099)	-64.3%	0.431 (0.357; 0.521)	-27.4%	0.878 (0.636; 1.210)			
<b>France</b>	-26.9%	0.712 (0.664; 0.764)	-20.8%	1.084 (0.821; 1.430)	-46.4%	0.488 (0.403; 0.591)	-26.7%	1.026 (0.828; 1.285)			
<b>Italy</b>	-35.2%	0.650 (0.615; 0.687)	-43.8%	0.867 (0.647; 1.161)	-54.6%	0.700 (0.574; 0.853)	-25.0%	1.131 (0.878; 1.437)			
<b>Spain</b>	-13.3%	0.859 (0.798; 0.924)	-50.0%	0.577 (0.392; 0.850)	-75.6%	0.281 (0.189; 0.419)	-7.3%	1.070 (0.790; 1.449)			

**Table 3.** Occurrence of Legionnaires' disease (LD) in index countries compared to European Union estimates for 2020 vs. 2019. Notes: HALD = hospital-associated LD, TALD = travel-associated LD; RR = relative risk; 95%CI = 95% confidence intervals.

	Total cases	HALD	TALD	DEATHS
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
<b>Germany</b>	1.123 (1.049; 1.202)	1.021 (0.714; 1.459)	1.074 (0.894; 1.290)	0.841 (0.617; 1.146)
<b>France</b>	0.992 (0.930; 1.059)	1.287 (0.992; 1.668)	1.613 (1.376; 1.890)	0.869 (0.706; 1.069)
<b>Italy</b>	0.880 (0.839; 0.905)	0.818 (0.617; 1.086)	1.366 (1.136; 1.643)	0.849 (0.673; 1.072)
<b>Spain</b>	1.176 (1.099; 1.258)	0.939 (0.638; 1.381)	0.733 (0.494; 1.090)	1.073 (0.803; 1.435)

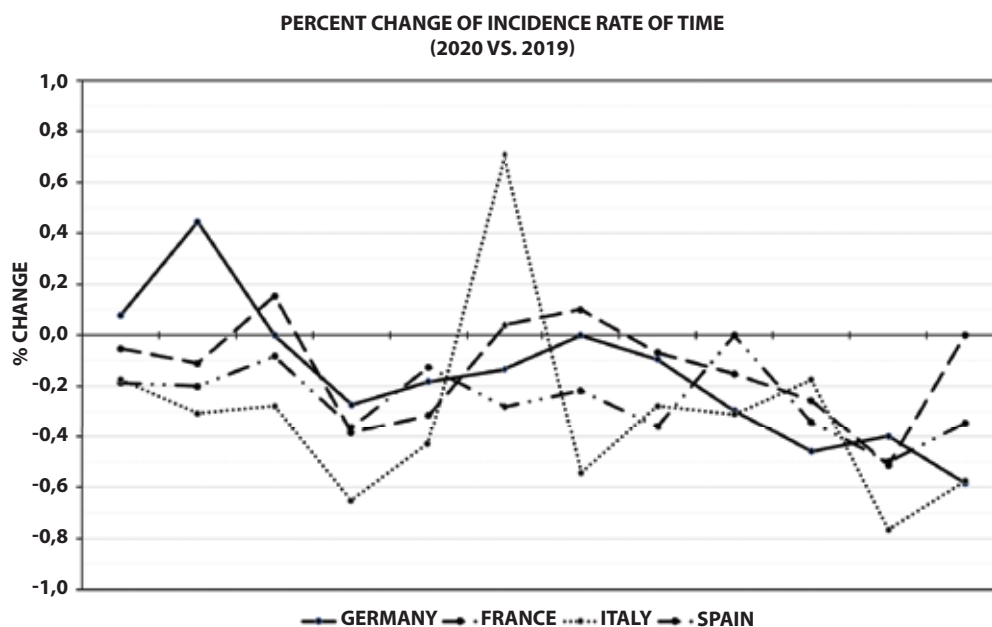
at EU-level. On the contrary, Germany (-17.2%) and Spain (-13.3%) exhibited a less pronounced drop, that resulted in an increased risk for new diagnoses (RR 1.123, 95%CI 1.049 to 1.202, and RR 1.176, 95%CI 1.099 to 1.258, respectively) (Table 3).

The seasonal trend for LD is reported in Figure 2. Briefly, after March 2020, when lockdown and NPI were diachronically implemented across EU, all the index countries experienced a sharp drop in monthly rates compared to 2019 (Figure 2a), that lasted until the end of 2020 for France and Germany. On the contrary, Italy and Spain experienced a resurgence in the month of June, substantially greater for Italy (+70.7%) compared to Spain (+4.0%), where it lasted until the end of July (+10.0%). When the monthly incidence rates were compared to the EU-level estimates for 2020 (Figure 2b), overall estimates for Italy and Spain

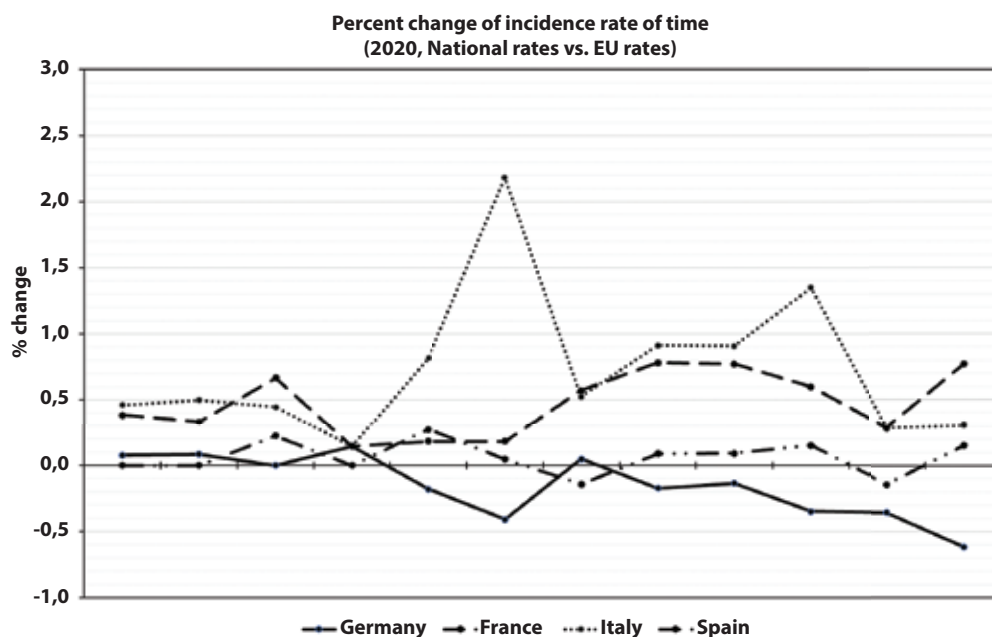
remained substantially higher across all the calendar year, particularly after the month of June.

Focusing on the main exposure groups, HALD decreased at EU-level by 38.4% in terms of crude figures, as the corresponding shares accounted to 5.1% of all new diagnoses at EU-level in 2020, compared to 6.1% in 2019, and 5.9% in 2015-2019 (RR 0.836, 95%CI 0.743 to 0.940). However, not only Spain alone reported a substantial decrease in HALD cases (RR 0.577, 95%CI 0.392 to 0.850), but no substantial differences were reported for all index countries, both when compared to estimates from 2019 (Table 2), and with EU (Table 3).

On the contrary, a drop in the TALD was reported not only at EU-level (-66.8%; RR 0.451; 95%CI 0.414; 0.490), but for all assessed countries, with some heterogeneities. For instance (Table 3), while the trend



A



B

**Figure 2.** Percent change of monthly incidence rates for the index countries (i.e. Germany, France, Italy, Spain), calculated as 2020 vs. 2019 (a) and 2020 vs. EU-level rates.

was similar to EU estimates for Germany (RR 1.074, 95%CI 0.894 to 1.290), and Spain (RR 0.733, 95%CI 0.494 to 1.090), in Italy (-54.6%) and France (-46.4%) the decrease was less pronounced. As a consequence, a proportionally increased risk in respect to EU estimates

was identified (RR 1.366, 95%CI 1.136 to 1.643, and RR 1.613, 95%CI 1.365 to 1.890, respectively).

The case fatality ratio (CFR) for EU was equal to 6.6% in 2020, being similar to the estimate for 2015 – 2019 (6.1%, RR 1.079, 95%CI 0.988 to 1.178), but

higher than that reported in 2019 (5.1%, RR 1.172, 95%CI 1.049 to 1.308). With a CFR of 9.0% in 2020, compared to 8.8% in 2019, and 8.7% in the timeframe 2015-2019, lethality for LD in France substantially exceeded all other estimates (RR 1.419, 95%CI 1.319 to 1.526,  $p < 0.001$ ), but no differences between 2020 and 2019 were identified, irrespective of the reference estimates (i.e. EU or national data). In other words, national CFR remained substantially stable across the assessed timeframe, not only when compared within the index countries for 2020 vs. 2019 (Table 2), but also when the estimates for lethality were compared to the general EU-level rates (Table 3).

## Discussion and Conclusions

During reporting year 2020, a sustained reduction in notification rates for LD was consistently identified, both at EU level and in all index countries (i.e. Germany, France, Italy, and Spain) (7–9,23,24). The decrease followed the implementation of NPI measures during the month of March 2020 (25). However, considerable heterogeneities were identified. On the one hand, despite a substantial surge during the month of June, Italy experienced an overall decrease in notification rates that exceeded EU-level estimates. On the other hand, the notification rates in Germany and Spain experienced a transitory increase (i.e. shortly before the inception of the pandemic, for Germany; after the month of June, for Spain) that has led to increased risk compared to EU estimates.

As LD has no inter-human spreading (14,26–28), NPI and lockdown measures cannot directly impair the diffusion of *Legionella* from the usual source of infection (i.e. contaminated aerosols produced in conjunction with water sprays, jets or mists), and alternative explanations are required. For instance, the reduction in notification rates may represent a drop in new patients, new diagnoses, or reported cases (8,28,29). Following the constraints of the pandemic, available may have been affected by considerable reporting issues, either directly (i.e. lack of diagnostic opportunities), or indirectly (i.e. lack of time to cope with the requirements of notification procedures). In this regard, Santé Publique France has recently reported an increase in

the selling of Urinary Antigen Tests for *Legionella pneumophila* in 2020 compared to 2019 (+30%), ruling out that the drop of reported cases may represent a drop in diagnoses rather than an actual reduction in incident cases (8). On the contrary, data on HALD, TALD, and CFR collectively suggest that 2020 was characterized by an actual reduction in new diagnoses.

The drop of notification rates was substantial for TALD, with crude figures that were nearly halved compared to the previous reporting year, with a 30% to 60% reduction compared to the previous 5-year time period. This trend can be explained through the global implementation of travel restrictions and general stay-at-home policies since the month of March 2020, with their progressive lifting during the warm season (6,17,30). Less opportunities for travels have led to a decrease number of stays in accommodation sites, with a subsequently decreased risk for *Legionella* infection from contaminated sources (31,32).

Even though HALD were similarly reduced in 2020 compared to 2019, when national rates were compared to EU estimates, the difference was substantial only for Spain. Such reduction was similarly not unexpected. The COVID-19 pandemic has forced healthcare providers to restrain the access to care, surgeries, and other hospital services not only for obvious issues associated with patient safety (i.e. avoid unnecessary exposures to environments that were potentially contaminated by SARS-CoV-2), but also because of the shortage of medical resources (33–35). In other words, the drop in HALD we were able to identify in 2020 compared to 2019 may represent the silver lining of the extensive delay or avoidance of medical care because of COVID-19.

Eventually, we identified a significant increase in the CFR at EU level that was not confirmed by the index countries. A possible explanation may be found in a combination of travel ban and saturation of health resources (36). While travel ban has reduced the share of cases occurring in travelers, whose younger age and better clinical status usually lead to a favorable outcome, the effect of the pandemic on diagnostic delays has been otherwise reported (33,34). In fact, a late diagnosis of LD is often associated with a dismal prognosis, particularly where ICU beds are scarcely available, a situation that has frequently occurred during the “first

wave” (i.e. March to May/June 2020). During 2020, all European countries have faced an unprecedented pressure on healthcare institutions, as medical assets were rapidly saturated by the requirements of the pandemic, but larger countries (such as Germany, France, Italy, and Spain) had a greater base on which rely on in order to expand their base capacity, irrespective of the economic resources (35). Not coincidentally, according to ECDC estimates, higher CFR for LD were identified in Greece (7.4%), Czechia (7.9%), and particularly in Denmark (13.7%), Hungary (19.8%), and Sweden (21.8%) (23).

Despite their potential interest, our study is affected by significant shortcomings. First and foremost, as we retrieved our estimates from National Bulletins, we were able to summarize and analyze only information preventively reported by National Authorities and/or ECDC. Our retrospective study shares therefore the implicit limits of all reviews and meta-analyses, being highly dependent on the parent studies (37,38), and affected by their quality and heterogeneity (38). Despite the common framework, some inconsistencies in the reporting strategies can be easily recognized, particularly when dealing with cases not included in the more usual diagnoses of HALD, TALD or even with cases associated with retirement homes (7). As confinement measures could have potentially increased the occurrence of new cases because of the prolonged exposure to potential sources, and the lack of proper maintenance interventions, an accurate reporting of community and work-related cases would radically improve our understanding of the actual epidemiology of LD during 2020 (39). Moreover, if the epidemiologic inquiry is not properly performed, and previous exposure to hospitals and/or accommodation sites are not accurately assessed, HALD or TALD cases may be wrongly accounted to community acquired cases, with consequential errors in eventual estimates (28,40).

In conclusion, our study suggests that during 2020 LD diagnoses have substantially dropped in the whole of EU. Available data substantially rule out that these estimates would represent the consequence of improper reporting or lack of diagnostic interventions. While NPI have hardly had any direct effect on the inter-human transmission of *Legionella*, travel ban has caused a sustained reduction in TALD, with noticeable

consequences on the overall estimates. In turn, the reduced availability of healthcare resources has possibly affected the occurrence of HALD, without a noticeable effect on the CFR of the countries that were specifically assessed in this report (i.e. Germany, France, Italy, Spain), and that are usually associated with high reporting rates for LD. ON the contrary, the increased estimates of CFR for the whole of EU suggest that the COVID-19 pandemic and its subsequent saturation of healthcare resources may have impaired a proper management of incident cases where less resources were available.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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## Supplementary material

**Supplementary Table 1.** Source of data included in the analyses.

Country	Total population (2021) No./TOT EU (%)	Reference Centre	Reference
Germany	83,121,363 (18.6%)	Robert Koch Institut	<a href="http://www.rki.de/DE/Content/Infekt/Jahrbuch/jarbuch_node.html">www.rki.de/DE/Content/Infekt/Jahrbuch/jarbuch_node.html</a>
France	65,235,843 (15.1%)	Santé Publique France	<a href="http://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/legionellose">www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/legionellose</a>
Italy	59,236,213 (13.3%)	Istituto Superiore di Sanità	<a href="http://www.epicentro.iss.it/legionellosi/epidemiologia-italia">www.epicentro.iss.it/legionellosi/epidemiologia-italia</a>
Spain	47,394,223 (10.6%)	Instituto de Salud Carlos III	<a href="https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/Legionelosis.aspx">https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/Legionelosis.aspx</a>
EU	447,007,596 (100%)	ECDC	<a href="https://atlas.ecdc.europa.eu/public/index.aspx">https://atlas.ecdc.europa.eu/public/index.aspx</a>