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WIDENING THE SCOPE FOR THE BURDEN OF COVID-19 – COMORBIDITIES AND LONG COVID: AN ANALYSIS OF THE THREE PANDEMIC YEARS IN LUXEMBOURG

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ABSTRACT – ***Objective:*** Burden of disease studies evaluate the direct impact of disease in terms of morbidity and premature mortality over a given time horizon. The objective of this study was to estimate the burden of COVID-19 in Luxembourg during the first three years of the pandemic, with a particular focus on methodologies applied to two areas of high uncertainty: post-acute consequences (PAC) of COVID-19 and the disparity of associated pathologies to COVID-19 deaths compared to other causes of deaths.

Materials and Methods: Epidemiological monitoring data on screening, hospital admission, and mortality associated with COVID-19 were used to estimate disability-adjusted life years (DALYs). Years of Life lost due to premature death (YLL) estimates have been adjusted for the impact of comorbidity profiles from cause-of-death data using the Charlson Comorbidity Index (CCI). In the absence of a PAC-specific disability weight, a symptom-based approach using data from a national cohort study was applied and compared with alternative weights used in the literature. A one-by-one sensitivity analysis was performed to evaluate the uncertainty associated with each model parameter.

Results: The total burden of COVID-19, including PAC, over three years, was estimated at 17,801 DALYs, combining 14,903 YLLs and 2,898 Years of Healthy Life lived with Disability (YLDs). Comorbidity adjustment led to an average reduction of 9% in YLL estimates. Alternative choices for PAC led to an up to 3-fold increase in YLD compared to our base case estimates. Prevalence, disability weight, and duration of PAC were the most influential parameters identified in the sensitivity analysis.

Conclusions: The COVID-19 pandemic has produced a significant burden on the resident population in Luxembourg. Adjusting for comorbidities is an important step in assessing the burden of COVID-19. The uncertainty associated with PAC parameters has highlighted the need for further research to standardize the definition of the prevalence, duration, and severity of this condition. The suggested symptom-based approach presents a flexible option until PAC-specific disability weights are derived in the future.

KEYWORDS: COVID-19, Burden of disease, DALY, Luxembourg, Long COVID, Comorbidity.

INTRODUCTION

On 30th January 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) regarding the rapid spread of a new virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was categorized as

a pandemic on 11th March 2020[1]. The resulting disease, called COVID-19 (COronaVIrus Disease 2019), is characterized by an acute respiratory infection that varies in severity from asymptomatic to severe form (requiring hospitalization or intensive care), and even fatal outcome[2]. Older age and the presence of comorbidities (e.g., cardiovascular diseases, diabetes, cancer, and chronic respiratory diseases) are known risk factors for severe COVID-19 infection and death[2,3]. Although most people recover from the disease, some might continue to experience symptoms or even develop new ones over the months following the infection. This phenomenon may be referred to as long COVID, post-COVID-19 condition, or, in this case, Post-Acute Consequences (PAC) of COVID-19. The most frequent symptoms in PAC are fatigue-related, but others usually reported include respiratory and cognitive complaints[4]. A recent national study tracked a cohort of resident adults with a polymerase chain reaction (PCR)-confirmed COVID-19 diagnosis over 12 months and identified fatigue, eye strain, shortness of breath, irritability, and anxiety as the most common symptoms[5].

The burden of disease methodology is a holistic approach for measuring the direct impact of illnesses on populations, measured by a composite indicator, called Disability-Adjusted Life Years (DALY). The DALY captures both non-fatal as well as fatal consequences of a disease, as a sum of two components: Years of healthy Life lived with Disability (YLD) to measure morbidity and Years of Life Lost (YLL) due to premature death to measure mortality. The DALY concept was first introduced in the 1990s by Murray et al[6] and has been widely used over the last two decades as a comprehensive way of assessing the relative impact of different diseases across different countries and over time.

The COVID-19 pandemic has posed significant stress on healthcare systems worldwide, as well as a heavy burden on the population, and Luxembourg is no exception. Performing a detailed analysis of this health crisis and its direct impact on the population's health is of utmost importance to learn lessons and to be better prepared for future challenges. An analysis of the burden resulting from the acute phase only is published in a national report[7]. The European Burden of Disease Network (burden-eu) has developed a consensus model to evaluate the burden of COVID-19[8], providing a basis for international comparisons on the health impact of COVID-19 during the pandemic. Nevertheless, estimations based on this model are highly dependent on several input parameters (i.e., prevalence, incidence, duration, disability weight of each health state), and results may lack comparability in case of missing consensus on the definition of these variables.

While most studies agree on the input variables for the acute phase, there are two areas of high variability in the assessment of the burden of COVID-19. One potential source of variability relates to the estimation of YLL. YLLs for a given death are based on the remaining life expectancy (RLE) conditional on the age at death. Existing RLE tables take into account comorbidities present in the general population[9]. However, individuals who died of COVID-19 had a higher prevalence of certain severe comorbidities compared to the general population[3], suggesting a shorter RLE. YLL calculations not considering differences in comorbidity profiles may, therefore, result in an overestimation of YLL and, consequently, of DALY.

Further, there appears to be no international consensus regarding the definition, prevalence, duration and disability weight (DW) associated with PAC[10]. While the DALY in COVID-19 is known to be driven mainly by premature mortality[11-13], the heterogeneity associated with PAC is extremely high and may have a significant impact on the morbidity component (YLD). A recent comprehensive meta-analysis identified 130 publications, with prevalence of long COVID-19 varying from 0% to 93%[10]. Studies using the European consensus model have either focused on the acute phase only or, where PAC was included, applied heterogeneous PAC durations from 28 to 269 days[14-17]. Most studies applied the suggested DW for PAC of 0.219[15,18,19] based on the disability associated with post-acute effects of an infectious disease. However, recent suggestions include alternative DW, for instance, based on moderate and severe anemia (0.052, 0.149)[20] to describe PAC as a less debilitating, fatigue-related health state.

Considering the fact that COVID-19 is an emerging infectious disease, it is important to identify and address uncertainties in the calculation of DALYs to demonstrate the robustness of the evidence produced and to enable valid comparisons between studies.

The primary objective of this study was to quantify the direct burden of COVID-19, measured in DALYs, in Luxembourg during the first three years of the pandemic (March 2020-March 2023), accounting for acute phase and post-acute consequences (PAC). As secondary objectives, a particular focus was given to methodological choices applied to two areas of high uncertainty: (A) to adjust remaining life expectancy (RLE) and YLL for comorbidities; (B) to compare alternative approaches to measure the burden caused by PAC. Alternative scenarios with regard to comorbidity and PAC were analyzed to evaluate the impact of methodological choices.

PATIENTS AND METHODS

Data

The study covered the resident population in Luxembourg to analyze the burden of COVID-19 over a three-year period, from 15th March 2020 until 14th March 2023.

The analysis relied on data from the nationwide COVID-19 monitoring system. Since the beginning of the pandemic, the health authorities in Luxembourg have set up a national surveillance platform that collects daily updates on laboratory test results, hospital admissions (normal and intensive care), and deaths associated with COVID-19 infection. These data underwent several steps of quality control before being stored in the Luxembourg Microdata Platform on Labour and Social Protection and linked daily to the national social security system to provide baseline characteristics on the individuals.

Additionally, the national causes of death registry records all deaths occurring in Luxembourg and includes up to six causes of death, which enabled an in-depth analysis of comorbidities in fatal COVID-19 cases.

Ethical statement

The planning, conduct, and reporting of the study was in line with the Declaration of Helsinki[21]. Official ethical approval and patients' consent were not required, as data collection is part of the national pandemic surveillance system set up under the authority of the Ministry of Health (now Ministry of Health and Social Security)[22]. All personal data were pseudonymized before treatment and were analyzed in a secured virtual environment to comply with the European General Data Protection Regulation[23].

Disease model

Infected individuals were assumed to experience a combination of health states, as defined in the consensus disease model[8]. Upon acute infection, individuals may develop asymptomatic, mild/moderate, severe, or critical disease. Symptomatic infections may lead to death or result in recovery or PAC (and the latter eventually in recovery). One infection may contribute to multiple health states over the course of the disease.

For the purpose of this study, the following definitions and assumptions were applied:

- COVID-19 infection case: any positive result in a PCR test or a clinical diagnosis indicating COVID-19 hospitalizations and deaths. All subsequent positive tests within a 90-day period were assigned to the same infection.
- COVID-19 asymptomatic case: all non-detected cases are assumed asymptomatic. In addition, 20% of COVID-19 infections are assumed asymptomatic[16].
- COVID-19 mild/moderate case: 80% of all COVID-19 infection cases are assumed to be mild/moderate[16]. Some of these progress to more severe health states.
- COVID-19 hospitalized case: any hospitalization due to COVID-19, according to clinical diagnosis or PCR assessment. To account for hospital transfers and relapses, we merged hospitalizations where a person was discharged and readmitted within 3 days (as long as COVID-19 remains the underlying cause).
- Severe COVID-19 case: any COVID-19 hospitalized case in the normal care unit.
- Critical COVID-19 case: any COVID-19 hospitalized case in the intensive care unit.
- COVID-19 death case: any registered death linked to COVID-19.
- PAC case: any COVID-19 infections leading to long-term consequences, defined as a proportion of all symptomatic COVID-19 cases (mild/moderate, severe, critical)[10].

Statistical analysis

Based on the applied disease model, we estimated the burden of COVID-19 using DALY, calculated as the sum of YLL and YLD[24].

YLL and comorbidities at death

YLLs were calculated as a summation of the product of the number of death cases (M) in the age group (i) and the age-specific RLE, as depicted in Equation 1:

$$YLL = \sum_{i} M_i \times RLE_i$$

RLE was based on the Global Burden of Disease (GBD) 2019 reference life tables[9]. Reduced life expectancy caused by chronic diseases is taken into account in the design of RLE tables. However, severe comorbidities have been found to significantly increase the risk of mortality from COVID-19[3]. This suggests that individuals who succumbed to this virus had a higher risk of short-term mortality compared to the general population. Our national surveillance data confirms a higher number of comorbidities in COVID-19 death cases compared to other causes of death. Neglecting these comorbidities poses a risk of overestimating RLE. Thus, we applied the Charlson Comorbidity Index (CCI)[25], in line with the methodology proposed by Arlotto et al[26] to adjust RLE among those who died from COVID-19 in this study. This index is based on the presence or absence of 17 selected comorbidities and helps forecast the probability of death

within one year. Each comorbidity is assigned a severity weight[27], and the sum of all comorbidity weights results in the individual CCI score, with higher scores indicating more comorbidities. To determine the risk of dying within 1 year, the equivalences described by Schneider et al[28] were used: 10% risk for 0 CCI score, 15% risk for 1-2 CCI score, 24% risk for 3-4 CCI score and 31% for ≥ 5 CCI score.

Based on the comorbidities identified in the national causes of death registry, a CCI score was computed for all death cases spanning from January 2020 to December 2022 (latest available data), and the average risk by age group was calculated for both COVID-19 and non-COVID-19 profiles. Finally, the ratio between the risks in these two profiles (RLE reduction coefficient) was used to adjust the RLE by age group (i), as outlined in Equation 2:

$$RLE\_adj_i = RLE_i \times min\left(\frac{risk\_base_i}{risk\_COVID_i}, 1\right)$$

YLD during the acute phase

YLD was calculated as a summation of the product of the number of cases (N) experiencing each health state (j: mild/moderate, severe, and critical infection), the disability weight (DW) of each health state, and the total duration (D) of each health state by age group (i), as outlined in Equation 3:

$$YLD_i = \sum_{ij} N_{ij} \times DW_j \times D_{ij}$$

According to the disease model, asymptomatic cases produced no disability and were excluded from the YLD calculation. Severe and critical cases were estimated as the number of hospitalizations (in normal and intensive care units, respectively). All symptomatic cases were assumed to pass through the mild/moderate health state. Mild/moderate counts were hence estimated as COVID-19 cases minus a correction factor of 20%; this is based on the surveillance performed in Malta[16]. Similar to Malta, Luxembourg implemented a large-scale testing strategy at the start of the pandemic, as well as exercised extensive contact tracing for COVID-19 infections, which allowed the identification of a proportion of asymptomatic, positive cases (estimated at 20%). Additionally, undetected cases during the pandemic were assumed asymptomatic and, consequently, caused no disability.

As suggested by the burden-eu guideline[8], the DWs from the GBD 2019 study for mild/moderate and severe cases[29] and the DW from the European Disability Weight study for critical cases[30] were applied.

In the absence of national data on the duration of symptomatic disease not requiring hospitalization, mild/moderate cases were assumed to last 7.8 days, based on the median duration found in previous studies[14,15,19,31,32]. The duration of severe and critical forms of COVID-19 was calculated as the mean length of stay in normal and intensive care units by age group based on our national surveillance data. Based on 5,000 resamples, 95% adjusted bootstrap percentile intervals were calculated to overcome the skewness in the data and the small sample size in some subgroups. A summary of all input parameters used to estimate YLL and YLD for the acute phase and PAC is shown in Table I.

YLD linked to post-acute consequences

YLD linked to PAC were calculated using the same Equation 3.

To date, there is no consensus concerning the frequency, symptoms, severity, and duration of PAC in COVID-19 cases. In this study, three different scenarios were applied as estimates for DWs associated with PAC: one scenario was based on the symptom profile observed in the national cohort[5,] while two alternative scenarios used surrogate DWs from other health states.

In the national cohort of COVID-19 patients, individuals were asked to fill out a self-reported questionnaire after a 12-month follow-up period including details on 62 potential symptoms. The study revealed a variety of symptoms, the more frequent being observed in patients with more severe initial COVID-19 infections.

Symptom-based DWs

A first approach, inspired by an Australian study[19], is proposed, utilizing the PAC symptoms distribution observed in the national cohort. Each self-reported symptom was assigned a DW from an equivalent health state reported by GBD[33]. Symptom frequencies in symptomatic cases were adjusted for those of asymptomatic cases (control group), assuming that asymptomatic infections do not lead to PAC[34] and can be used as a proxy of symptoms in the general population. This adjustment is necessary to ensure the inclusion of symptoms related to PAC only. Only symptoms with a higher prevalence in the symptomatic onset group compared to the asymptomatic onset group were included. Finally, we calculated the aggregated DW for PAC as a weighted mean taking into account individual symptom frequencies.

Table I. Burden of disease model parameters.

Parameter		Base case	Lower limit	Upper limit	Source
Disability weights – acute phase					
Mild/Moderate		0.051	0.032	0.074	Wyper et al[8]
Severe		0.133	0.088	0.190	
Critical		0.655	0.579	0.727	
Duration – acute phase, in days					
Mild/Moderate		7.8	7.0	14.0	Several studies[14,15,19,31,32]
Severe, by age groups	0-19 years	2.7	2.4	3.1	National surveillance platform
	20-39 years	5.8	5.2	6.9	(mean, 95% confidence interval
	40-59 years	8.9	8.2	10.1	by bootstrapping)
	60-79 years	12.3	11.6	13.1	
	80+ years	14.3	13.5	15.1	
Critical, by age groups	0-19 years	9.3	3.3	23.3	National surveillance platform
	20-39 years	10.7	7.4	18.7	(mean, 95% confidence interval
	40-59 years	15.9	13.8	18.7	by bootstrapping)
	60-79 years	15.6	13.9	17.7	
	80+ years	9.2	7.9	10.9	
PAC parameters					
Disability weight					
Symptom-based DWs (by onset severity)	Mild/Moderate	0.063	0.037	0.095	Fischer et al[5]
	Severe	0.071	0.043	0.106	
	Critical	0.071	0.043	0.106	
Anaemia-based approach (by onset severity)	Mild/Moderate	0.052	0.034	0.076	Wyper et al[20]
	Severe	0.149	0.101	0.209	
	Critical	0.149	0.101	0.209	
Consensus model		0.219	0.148	0.308	Wyper et al[8]
Duration, in months		12	6	24	Fischer et al[5],
Prevalence		13.6%	1.2%	68.0%	Woodrow et al[10]
Comorbidity parameters					
RLE reduction coefficient, by age group	0-44 years	1.00	1.00	1.00	National causes of death registry
	45-49 years	0.82	0.57	1.00	
	50-54 years	0.96	0.77	1.00	
	55-59 years	0.94	0.87	1.00	
	60-64 years	0.88	0.76	1.00	
	65-69 years	0.80	0.72	0.88	
	70-74 years	0.91	0.82	0.99	
	75-79 years	0.88	0.81	0.96	
	80-84 years	0.92	0.86	0.97	
	85-89 years	0.92	0.88	0.95	
	90-94 years	0.94	0.90	0.98	
	95+ years	0.97	0.91	1.00	
Other input parameters					
Asymptomatic among detected (%)		20%	0%	40%	Hypothesis

DW: disability weight, RLE: remaining life expectancy, PAC: post-acute consequences.

The resulting value represents the DW incorporating an average number of two symptoms, as reported in a Danish study[13].

Equation 4

$$DW_{PAC} = 2 \sum_k DW_k \frac{\max(0, p_k - p\_asym_k)}{\sum_k \max(0, p_k - p\_asym_k)}$$

Where DW_k is the disability of symptom *k; p* and *p_asym* refer to the symptom prevalence in the symptomatic and asymptomatic groups, respectively. Separate DWs were derived for PAC cases according to mild/moderate and severe/critical disease onset. This approach is used for our base case analysis and is referred to "Symptom-based DWs".

Surrogate-based DWs

The European burden of disease network[8] recommended adopting specific disability weights for COVID-19 health states, derived from the European Disability Weight Study (EDWS) and the GBD 2019 study.

The authors suggested a DW of 0.219 for PAC, which originated from post-dengue chronic fatigue syndrome, a health state described as "Is always tired and easily upset, the person feels pain all over the body and is depressed"[29]. Similar to previous studies[14-17,19,31] and to support comparability of COVID-19 burden estimates, this DW value was applied in the analysis and referred to "consensus model", as shown in Table I.

An alternative suggestion by Wyper et al[20] proposed new DWs for PAC cases whose predominant symptom is fatigue [i.e., 0.052 (mild/moderate onset), 0.149 (severe and critical onset)], based on the similarities with anemia health states. This approach was named "Anemia-based approach" in our analysis (Table I).

Prevalence and duration of PAC

Concerning the frequency of cases, no national data evaluating the prevalence of PAC is so far available. Therefore, estimations from the meta-analysis by Woodrow et al[10] were used suggesting a prevalence of 13.6% (predictive interval 1.2% to 68.0%) among studies using routine healthcare records.

The model assumes a PAC duration of 12 months, in line with the time point of symptom reporting in the national cohort study.

All DWs and durations for the acute phase and PAC with related sources are also displayed in Table I.

Uncertainty

Parameter uncertainty was assessed using a one-by-one sensitivity analysis and methodological uncertainty was assessed in scenario analyses.

In a one-by-one sensitivity analysis the uncertainty in the input parameters was assessed by individually varying the disability weights (DWs) and durations of all health states, the prevalence of PAC, the percentage reduction in life expectancy due to CCI, and the assumed proportion of asymptomatic cases among detected cases, adjusting each parameter to its minimum and maximum values (Table I). Results are graphically displayed in a tornado plot, showing the relative importance of each variable, in terms of deviation from the base case estimate when varying their input values.

Alternative scenarios with regards to comorbidity and PAC were analyzed to evaluate the impact of methodological choices. Outcomes adjusted for comorbidities as proposed in this study were compared to outcomes not adjusting for comorbidities. The disability associated with PAC based on the national approach was compared to the consensus model, the anemia-based disability weights as well as no PAC at all.

All statistical analyses were performed with R® [version 4.3.1, R Core Team (2023), Vienna, Austria] and RStudio® [version 1.1.383, Posit team (2024), Boston, MA, USA].

RESULTS

Number of COVID-19 cases

Between 15 March 2020 and 14 March 2023, 369,648 COVID-19 cases were detected. Among those, 295,718 were mild/moderate cases, 4,710 were severe, 650 were critical, and 1,201 led to death.

Analysis of comorbidities

The analysis showed that 50% of COVID-19 deaths were associated with at least one comorbidity listed in the CCI. Dementia emerged as a prominent comorbidity (16%), followed by cancers (9%), chronic pulmonary disease (9%) and diabetes (7%). In addition, several other comorbidities not listed in the CCI were also notable contributors to COVID-19 deaths, including hypertension (9%), obesity (4%), cardiac arrhythmia (4%), and other neurological disorders (4%).

The comparison of CCI scores between COVID-19 deaths and baseline deaths (i.e., all other deaths except COVID-19) is illustrated in Figure 1a. Notably, CCI scores were significantly elevated for individuals aged between 65 and 94 years who died from COVID-19, confirming an increased comorbidity in this specific age group. The high uncertainty observed in middle-aged individuals (45-49 years old) is due to the low number of COVID-19 deaths, rendering it challenging to draw conclusions in these age groups. The percentage of RLE reduction subsequent to comorbidity adjustment, is depicted in Figure 1b. No RLE correction is implemented for individuals below the age of 45, as no severe comorbidities are observed. For those aged 50 and above, an average reduction in RLE of approximately 5-20% was observed. The age group of 65-69 experiences the most significant impact, with a 20% reduction in RLE [95% CI = (12%, 28%)]. This age group has the highest CCI scores, as almost 90% of COVID-19 deaths in this age group have at least one CCI linked comorbidity. Overall, considering comorbidities in COVID-19 deaths yielded an average reduction of 9% in YLL [95% CI = (7%, 12%)]. A sex-specific analysis did not unveil significant disparities in comorbidity patterns between men and women.

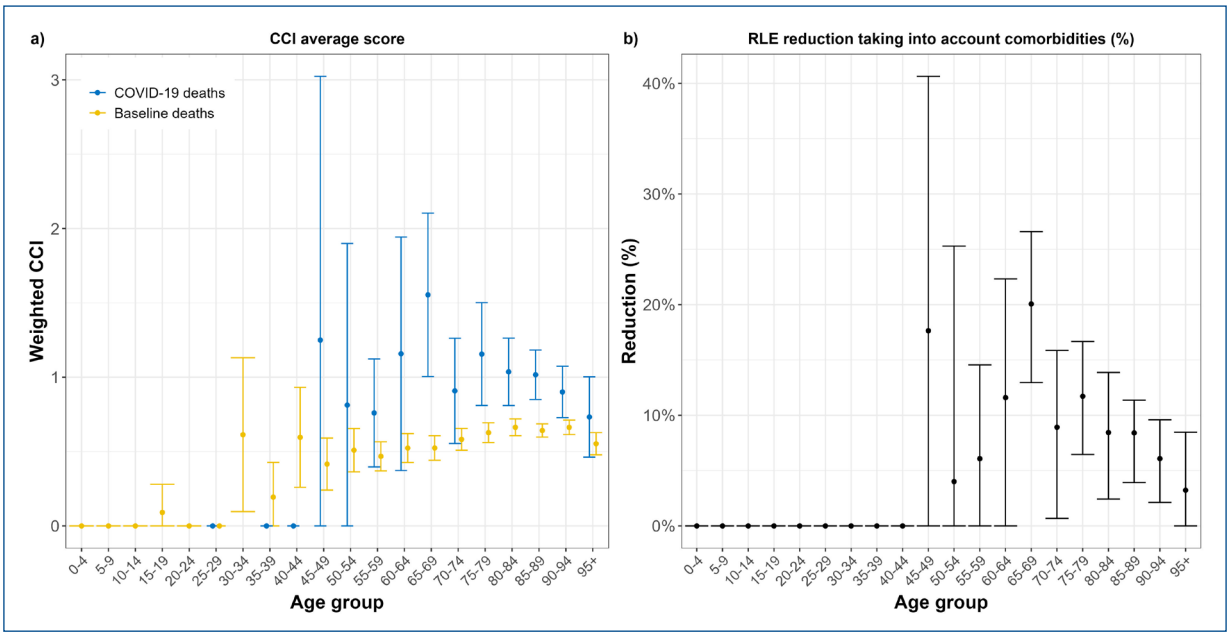

Figure 1. **a**, CCI scores from comorbidities at death by age group, for COVID-19 deaths and baseline deaths with 95% confidence intervals. **b**, Estimated percentage of reduction of RLE by taking into account comorbidities at death by age group with 95% confidence intervals. CCI: Charlson Comorbidity Index, RLE: remaining life expectancy.

Analysis of the direct impact of COVID-19

In our base-case analysis, the total burden of COVID-19 was estimated for the resident population in Luxembourg over the first three years of the pandemic. YLL outcomes were adjusted for comorbidities, and DWs associated with PAC were based on the symptoms observed in the Luxembourgish cohort[5]. A total of 17,801 DALYs, combining 14,903 YLLs and 2,898 YLDs were estimated. The total burden was highest during the first year, in men and in people aged 80 years and older. In contrast, women, especially individuals younger than 60 years, had a higher YLD when compared with other groups.

Detailed results by pandemic year, sex, and age group are displayed in Table II.

Table II. Estimates of the direct impact of COVID-19 in Luxembourg: DALY, YLD and YLL in total crude numbers and annual rate per 100,000 population.

	YLD		YLL		DALY	
Total	**Total crude number 2,898**	**Annual rate 152**	**Total crude number 14,903**	**Annual rate 782**	**Total crude number 17,801**	**Annual rate 934**
By pandemic year						
15 March 2020 – 14 March 2021	445	71	7,794	1,245	8,240	1,316
15 March 2021 – 14 March 2022	1,077	170	3,526	556	4,603	725
15 March 2022 – 14 March 2023	1,376	213	3,582	555	4,958	768
By sex						
Male	1,386	144	8,895	927	10,281	1,071
Female	1,512	160	6,008	635	7,520	794
By age group (years)						
0-19	679	168	0	0	679	168
20-39	943	168	345	62	1,289	230
40-59	889	160	2,023	364	2,912	524
60-79	286	92	6,423	2,072	6,709	2,164
80+	101	133	6,111	8,099	6,212	8,232

DALY: disability-adjusted life years, YLD: years of life lost due to disability, YLL: years of life lost.

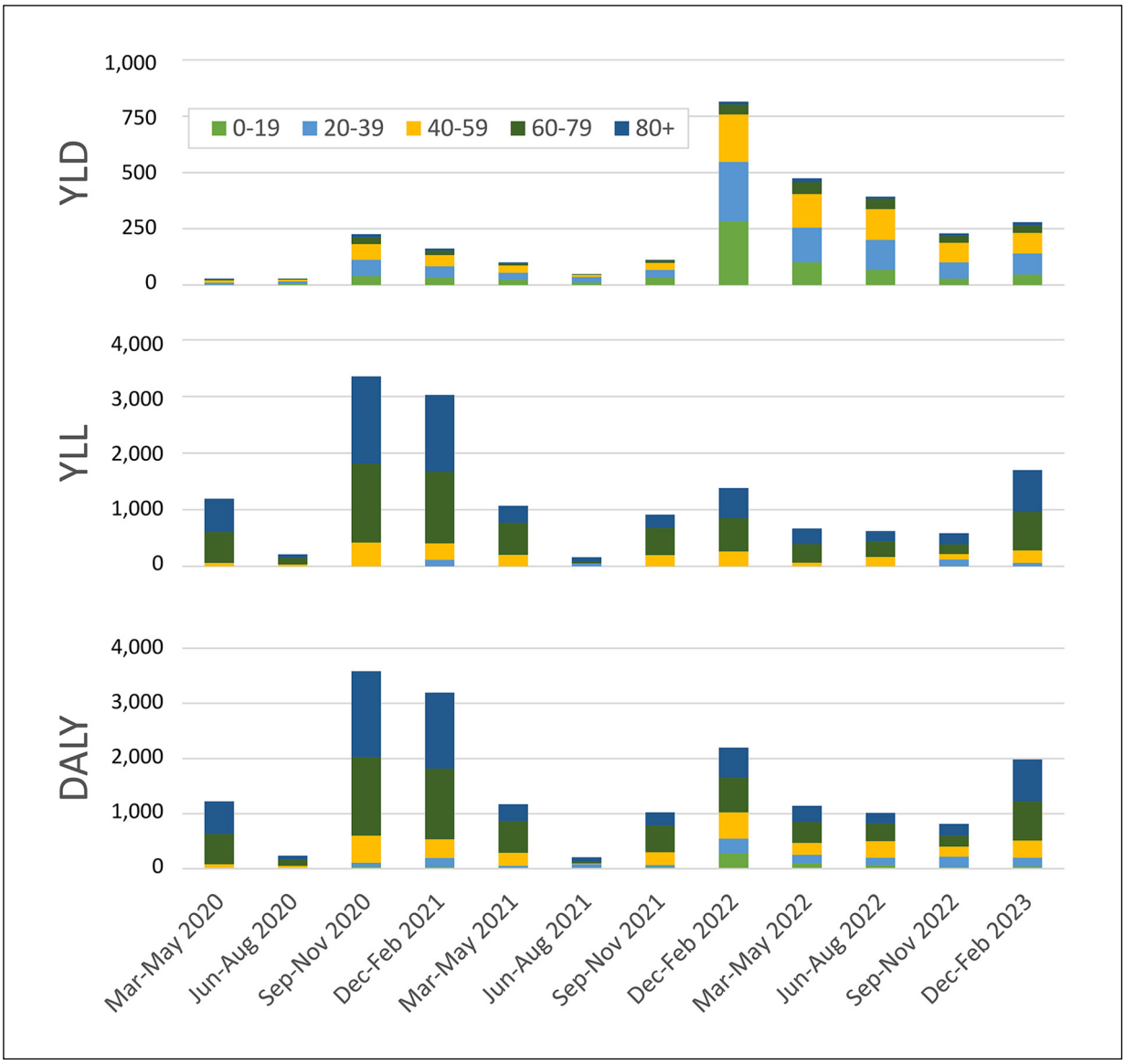

Figure 2. The evolution of the burden in terms of YLD, YLL and DALY by age group and over time in Luxembourg. DALY: disability-adjusted life years, YLD: years of life lost due to disability, YLL: years of life lost.

Results were further stratified into three-month periods to follow the burden of disease over time throughout the 3-year pandemic (Figure 2). YLL contributions dominated DALYs; both showed a very similar trend over time, with the highest impact during the autumn and winter of the first year of the pandemic (September 2020-February 2021), and most YLLs were attributed to the older age groups throughout the pandemic. YLDs, on the other hand, were highest during the last pandemic year, starting in December 2022, a period characterized by the large increase in the number of infections caused by the Omicron variant. Years of life lived with disability (YLD) were more important among younger age groups compared to older age groups.

One-Way sensitivity analysis

Table III shows changes in DALY, YLL, and YLD estimates as individual input parameters vary according to their likely lowest and highest values. Comorbidity adjustment was the only parameter impacting YLL; all other parameters impact YLD exclusively. Parameters associated with the highest impact on total DALYs were those relating to PAC: the prevalence of PAC, the DW associated with PAC, and the duration of PAC. Comorbidity adjustment was the 4th most influential parameter.

A Tornado Plot illustrates the impact of uncertainty by parameter in the overall results and by year of pandemic (Figure 3). When looking at an annualized analysis, the impact of comorbidity adjustment is the strongest in the first year of the pandemic (3rd place), where most death cases were observed. In

Table III. One-way-sensitivity-analysis results: YLD, YLL and DALY based on lowest and highest value of uncertain input parameters compared to base-case results.

Base case results	YLD = 2,898		YLL = 14,903		DALY = 17,801	
Range	Lower	Upper	Lower	Upper	Lower	Upper
PAC prevalence	582	13,059	NA	NA	15,485	27,962
PAC DW	358	9,166	NA	NA	15,260	24,068
PAC duration	1,628	5,438	NA	NA	16,531	20,341
Comorbidity adjustment	NA	NA	13,673	15,958	16,571	18,856
Asymptomatic proportion	3,612	2,184	NA	NA	18,515	17,087
Mild duration	2,865	3,154	NA	NA	17,768	18,057
Mild DW	2,778	3,043	NA	NA	17,681	17,946
Severe DW	2,892	2,906	NA	NA	17,794	17,809
Critical duration	2,896	2,901	NA	NA	17,799	17,804
Critical DW	2,896	2,900	NA	NA	17,799	17,803
Severity duration	2,897	2,900	NA	NA	17,800	17,802

DALY: disability-adjusted life years, PAC: COVID-19 post-acute consequences, YLD: years of life lost due to disability, YLL: years of life lost, DW: disability weight.

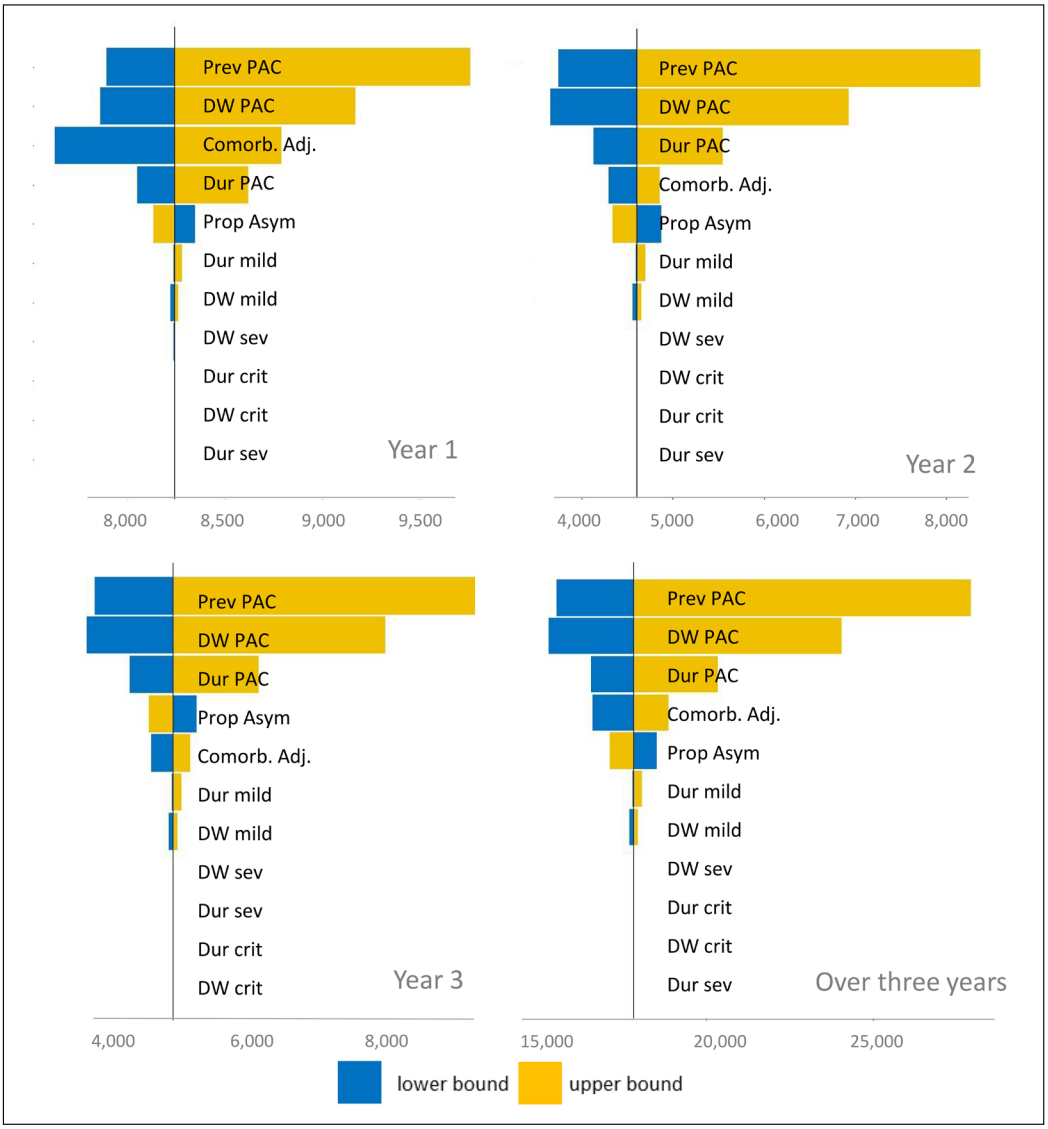

Figure 3. Tornado Plot: Illustrates impact of one-way uncertainty analysis by year of pandemic. Year 1: 15 March 2020-14 March 2021; Year 2: 15 March 2021-14 March 2022; Year 3: 15 March 2022-14 March 2023. Asym: asymptomatic, Comorb. Adj.: comorbidity adjustment, crit: critical, Dur: duration, DW: disability weight, PAC: COVID-19 post-acute consequences, Prev: prevalence, sev: severe.

the second and third years of the pandemic, comorbidity adjustment moved to 4th and 5th place, behind the duration of PAC and the proportion of asymptomatic cases among the detected cases. Uncertainty in the duration and DW associated with mild/moderate, severe, and critical cases was very small.

Scenario analyses

Different scenario analyses evaluated the impact of comorbidity adjustment and DWs associated with PAC (Figure 4).

The adjustment of RLE for comorbidities impacted YLL estimates; adjustment for comorbidities decreased the estimated YLL by 9% compared to no adjustment.

Alternative approaches to estimating the DW associated with PAC showed major impacts on the YLD component of the DALY. Compared to the symptom-based scenario, applying the anemia-based DWs yielded relatively similar results, with a decrease of 13% in YLD, while the DWs applied in the consensus model increased YLD by over 300%. Analyzing the acute phase only led to an 88% reduction in YLD estimates compared to our base case approach.

DISCUSSION

To our best knowledge, this is the first study evaluating the direct impact of COVID-19 on the health of the resident population in Luxembourg, during the acute phase and on post-acute consequences. Over the first three years of the pandemic, we estimated 17,801 DALYs (934 DALYs/100,000 inhabitants per year). Globally, YLL represented 84%, and it was higher in older age groups particularly in men. YLD was slightly higher in women and its relative contribution to the DALY increased over time (from 5% in year 1 to 28% in year 3).

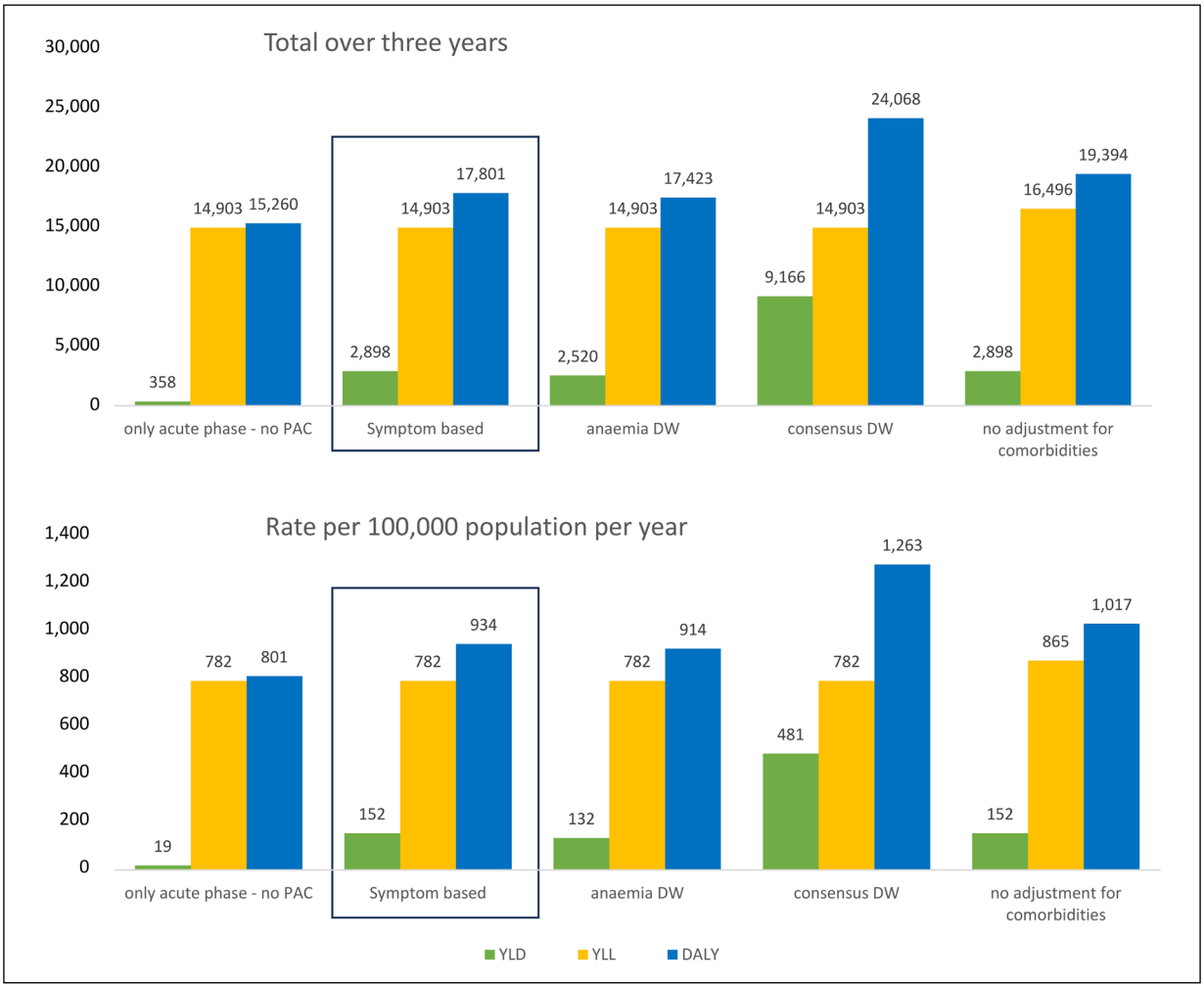

Figure 4. Scenario analyses: Estimated DALY, YLD and YLL in total crude numbers over three years (top) and annual rate per 100,000 population (bottom). Scenarios: Acute phase only, symptom-based disability weights (base case analysis), anemia-based disability weights, consensus model disability weights, not adjusting for comorbidities. DALY: disability-adjusted life years, DW: disability weight, PAC: COVID-19 post-acute consequences, YLD: years of life lost due to disability, YLL: years of life lost.

In the European context, several studies have been published covering the burden of COVID-19, and a subset of these evaluated the impact of PAC[11,12,14-16,18]. The burden estimations in these European studies ranged from 883 to 2,614 annualized DALY/100,000 (Sweden and Belgium, respectively)[11,18], with Luxembourg (1,251) below the mean (1,512). All studies included at least the first 10-12 months of the pandemic and applied the DW of the consensus model. Most assumed a duration of PAC cases of 28 days, which differs significantly from the WHO definition (minimum duration of 5 months after the infection)[4]. Compared to the burden from the acute phase only, the inclusion of PAC in these studies entailed a median DALY increase of 1.0%. In our analysis, this increase was 4.8%, which can be explained by the fact of uncertainty from PAC parameters having the highest impact in the estimations' variation, as well as by the longer time horizon (12 months).

The strength of our study resides in the good quality and national representativeness of the data, as well as the specifications and assumptions of the disease model used. Infection cases in our analysis were those reported within the national monitoring system, identified either based on a positive PCR test or a clinical diagnosis of cases with more severe outcomes (hospitalization or death). Rapid (lateral flow) tests were not included, which may have led to an underestimation of positive COVID-19 cases, especially towards the later stages of the pandemic, where self-testing was more common and not always followed by a PCR test. Nevertheless, we assume these cases to be mild or asymptomatic, as more pronounced symptoms would mostly have led to a primary health care consultation confirming the infection with a PCR test or hospital admission in more severe cases.

Life tables used for the estimation of YLL assume the same age-specific RLE for everyone. The role of baseline health as a predictor for severe outcomes, however, creates an imbalance in this assumption, as severe comorbidities occur more often in the population with the disease, reducing their baseline RLE compared to the general population. This analysis has used national registry data on causes of death to evaluate the impact of this imbalance. We have adjusted RLE to produce a more realistic estimation of the impact of COVID-19 on YLL. We found an overestimation of YLL of around 11% when not adjusting for comorbidities, which could constitute a significant impact on the disease burden, particularly in diseases mainly driven by the years of life lost due to premature death.

Given the relative novelty of COVID-19, little consensus exists on the definition, duration, and disability weights associated with PAC. The European consensus model[8] provides a strong foundation for ensuring sound methodology and comparability across analyses conducted in different locations. Our analysis has emphasized the extent of remaining uncertainty related to the choice of input variables, notably with regard to PAC. This study assessed the impact of various assumptions related to PAC, highlighting the key drivers of uncertainty in the evaluation of the burden of COVID-19. This indicates a strong need to harmonize the definition of PAC in the context of GBD studies beyond the current definition from WHO[4]. This would help reduce ambiguity regarding the occurrence of PAC symptoms, their severity, and their duration, which could eventually improve assessment and international comparability between studies. Although there are currently no well-defined PAC-specific disability weights, most PAC-associated symptoms are not exclusive to COVID-19 and could be derived from other diseases as surrogates. The European consensus[7] proposes the use of DW associated with post-dengue chronic fatigue syndrome, while Wyper et al[19] propose the use of anemia-based DWs. The lack of a PAC-specific DW and the fact that symptom profiles vary widely across patients, make the symptom-based approach, as applied in this base case, a suitable option. Our results are similar to those derived by applying the anemia-based weights.

This study sought to identify the main sources of uncertainty in DALY calculations, quantify and analyze the potential related bias in order to help further understand estimates, and support effective cross-comparison and relevant knowledge transfer of evidence.

Our estimation of DW for PAC has its limitations. It is based on data collected from 289 participants who fully completed a 12-month questionnaire following acute COVID-19 infection[5], while symptomatology in long COVID-19 may evolve over time. Further, the response rate was limited, and the control group (individuals with asymptomatic infection) was small.

Concerning the analysis of comorbidities, the data available in the registry allowed for the reporting of up to six comorbidities, hence the completeness of comorbidity profiles cannot be guaranteed. The CCI is an acknowledged measure evaluating the influence of comorbidities on short term death by taking into account a selection of 16 diseases and age; however, the influence of other diseases may also play a role in the context of COVID-19. Comorbidities, which are potential direct complications of COVID-19 with no men-

tion of a chronic disease (heart attack, stroke and renal insufficiency) have been excluded from the analysis. Therefore, this analysis may still underestimate the true impact of comorbidity imbalance.

CONCLUSIONS

The COVID-19 pandemic posed a significant burden to the population in Luxembourg in terms of DALYs, particularly during the first year. The findings of this study demonstrate a high degree of variability in estimates, depending on the parameters applied, underlining the need for standardization. This is particularly important concerning long COVID-19, for which further research is needed to better understand it in terms of definition, occurrence of symptoms, duration, and disability weights of PAC.

Conflict of Interest

The authors have no conflict of interest to declare.

Authors' Contribution

SS, JW, DA and AA: Conceived, designed the analyses, and drafted the manuscript. SP provided methodological advice on burden of disease approach. SP, SM, MD, AA: contributed to the critical and intellectual revision of the manuscript. All authors approved the final version.

Ethics Approval

The planning, conduct and reporting of the study is in line with the Declaration of Helsinki. Official ethical approval is not required as data collection is part of the national pandemic surveillance system set-up under the authority of the Ministry of Health.

Informed Consent

Patients' consents are not required as data collection is part of the national pandemic surveillance system set-up under the authority of the Ministry of Health.

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Availability of Data and Materials

Due to the nature of the research, which is based on large-scale national individual data, supporting data is not available publicly.

AI Disclosure

The authors declare that no form of generative artificial intelligence was used for writing the manuscript.

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