Incidence and Risk Factors of Illnesses Presumably Caused by A SARS-CoV-2 Infection in The General Population During The Lockdown Period: A Multi-Cohort Study.

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Abstract

Background Our main objectives were to estimate the incidence of illnesses presumably caused by SARS-CoV-2 infection during the lockdown period and to identify the associated risk factors.

Methods Participants from 3 adult cohorts in the general population in France were invited to participate in a survey on COVID-19. The main outcome was possible COVID-19, defined as a sudden onset of cough, fever, dyspnea, ageusia and/or anosmia, that lasted more than 3 days and occurred during the 17 days before the survey. We used delayed-entry Cox models to identify associated factors.

Results Between April 2, 2020 and May 12, 2020, 279,478 participants were invited, 116,903 validated the questionnaire and 106,848 were included in the analysis. Three thousand thirty-five cases of possible COVID-19 were reported during 62,099 person-months of follow-up. The cumulative incidences of possible COVID-19 were 6.2% (95% Confidence Interval (95%CI): 5.7%; 6.6%) on day 15 and 8.8% (95%CI 8.3%; 9.2%) on day 45 of lockdown. The risk of possible COVID-19 was lower in older age groups and higher in French regions with a high prevalence of SARS-CoV-2 infection, in participants living in cities >100,000 inhabitants (vs rural areas), when at least one child or adolescent was living in the same household, in overweight or obese people, and in people with chronic respiratory diseases, anxiety or depression or chronic diseases other than diabetes, cancer, hypertension or cardiovascular diseases.

Conclusion The incidence of possible COVID-19 in the general population remained high during the first two weeks of lockdown, and decreased significantly thereafter. Modifiable and non-modifiable risk factors were identified.

Introduction

Following the identification of a novel coronavirus (SARS-CoV-2) in Wuhan, China in December 2019 and its worldwide spread, the first imported COVID-19 cases were initially reported in France on January 24, 2020. Less than two months later, the French government declared a nationwide epidemic (phase 3) and a generalized lockdown procedure was set-up on March 17, 2020. Public health reports have shown that lockdown had a marked impact on the dynamics of the pandemic with a clear downward trend in new hospitalizations from April 1, 2020, and a consecutive decrease in the number of deaths from April 7, 2020.[1,2] Thus, the French government eased these restrictions on May 11th. Although there is obvious epidemiologic evidence that the lockdown period had a significant impact on severe COVID-19, estimates of its impact on mild-to-moderate COVID-19 are based on modelling studies,[3] and are not yet supported by clinical evidence.

Our main goals were 1) to estimate the incidence of illnesses presumably caused by SARS-CoV-2 infection during the lockdown period; 2) to identify the associated risk factors. We also described associated symptoms, preventive behaviors and healthcare in relation to these illnesses.

Participants And Methods

Design

The SAPRIS (“SAnté, Perception, pratiques, Relations et Inégalités Sociales en population générale pendant la crise COVID-19”) survey was begun in March 2020 to evaluate the main epidemiological, social and behavioral challenges of the SARS-CoV2 epidemic in France in relation to social inequalities in health and healthcare. SAPRIS is based on a consortia of prospective cohort studies involving two child-cohorts (not presented in this study) and three general population-based adult cohorts: CONSTANCES, a “general population” cohort including a representative sample of 215,000 adults (including 66,000 followed by internet) aged 18 to 69 at inclusion and recruited from 2012;[4] E3N / E4N, a multigenerational adult cohort based on a community of families with 113,000 participants (women recruited in 1990 and still actively followed-up, their offspring and the fathers of these offspring) among whom 90,000 have been invited to an internet follow-up;[5] and NutriNet-Santé a nutritional general population-based internet cohort started in 2009, with 170,000 included participants.[6]

Ethics and public involvement

Ethical approval and written informed consent was obtained from each participant before enrolment in the original cohort. According to French law, the present nested survey did not require specific additional written consent from the participant. It was approved by the Inserm ethics evaluation committee (approval #20-672 dated March 30, 2020). Representatives of the participants tested and validated the questionnaires, but they did not contribute to other aspects related to the design, conduct, reporting or dissemination of the research.

All participants from the original cohorts with regular access to electronic (internet) questionnaires were invited to participate in the current SAPRIS survey (figure 1). A first self-administered questionnaire covered the lockdown period and was sent from April 1, 2020 and returned before May 12, 2020. A second questionnaire covered the post-lockdown period and was sent between May 5, 2020 and June 15, 2020. The present study used the data from the first self-administered questionnaire, which included questions on socio-demographics, household size and composition, SARS-CoV2 diagnosis, a detailed description of the subject’s symptoms in the two weeks before the questionnaire, comorbidities, healthcare use and treatment, employment, daily life, child care, alcohol, tobacco and cannabis use, social and sexual life, preventive measures, risk perception and beliefs.

Additional specific socio-demographic and clinical characteristics were extracted from original cohort databases. Symptoms were reported if they had been present at least once in the last 14 days. If a symptom had been, but was no longer present when the questionnaire was completed, the duration was noted on a scale (less than 1 day, 1 to 3 days, 4 to 7 days, 8 to 14 days, >14 days). Finally, the total time (in days) between the onset of the first symptoms and the questionnaire was reported. All visits outside the home and the use of preventive measures in the 7 days before the questionnaire were reported.

Outcome

The main outcome was possible COVID-19, defined according to the European Centre for Disease Prevention and Control as at least one of a cough, a fever, a dyspnea, a sudden onset of anosmia, ageusia or dysgeusia,[7] that lasted more than 3 days and occurred during the at-risk period. Participants were also requested to report the occurrence of cough, fever or dyspnea before March 1, 2020 or between March 1 and the two weeks before the questionnaire, and whether they or any other household members had tested positive for SARS-CoV-2 since the beginning of the pandemic. The primary "at-risk period" was defined as the 17 days before the self- administered questionnaire for each patient, corresponding to the 14 days to report the presence of symptoms, plus 3 days for the minimum duration of our definition of possible COVID-19. In a first sensitivity analysis, no restriction was made on the minimum duration of symptoms, extending our primary case-definition of possible COVID-19 to illness that lasted less than 4 days. In a second sensitivity analysis, the at-risk period was defined as between March 16, 2020 and the date of the questionnaire for all participants. This definition made it possible to include all possible COVID-19 that occurred during the lockdown period.

Covariates

We explored the association of possible COVID-19 with age, gender, address location, French metropolitan regions, number of people living in the household, number of children in the household**,** educational level, professional activity before lockdown, job position, professional activity during lockdown, BMI, chronic conditions (according to a pre-specified list). Age groups were categorized according to predefined limits (<40; 40-49; 50-59; 60-69; ≥70 years) and BMI according to standard cut-offs (<18.5; 18.5-<25; ≥25-<30; ≥30 kg/m^2).[8]

Statistical methods

We determined that 100,000 subjects were needed to have a power of at least 80% to identify associations (Odds-Ratio, OR <0.9 or OR >1.1) between covariates and possible COVID-19 in a wide range of situations, assuming 10% of events and 10% to 90% exposure.

We used inverse probability weighting to correct for selection bias (when only a subgroup of the whole cohort was invited to participate by internet) and inverse probability weighting to correct for non-participation bias in those who were invited. Weights were estimated using logistic regression models, with selection or participation as the response variables, and socio-demographic characteristics as covariates. Unweighted and weighted daily incidence rates of possible COVID-19 and 95% confidence intervals were estimated with an exact method based on the Poisson distribution. Estimates of unweighted and weighted cumulative incidences on days 15 (March 30, 2020), 30 (April 14, 2020) and 45 (April 29, 2020) of lockdown were obtained as one minus the estimated probability of survival free of possible COVID-19 at that time.

To account for potential heterogeneity between the cohorts, left-truncation and censorship in the data, factors associated with the occurrence of possible COVID-19 were identified using unweighted data and delayed-entry Cox models with stratification on the source cohort. The start of the at-risk period was

defined according to the calendar day for each participant and survival time was calculated as the time between that day and the day the questionnaire was filled-out in case of no symptom or the day the first symptoms were reported in possible COVID-19 cases. Multivariable analysis was performed including all factors associated with possible COVID-19 cases on univariable analysis. All analyses were performed with SAS 9·4 software (SAS Institute Inc., Cary, North Carolina, USA). A P-value <.05 was considered to be statistically significant.

Results

A total of 116,903 of the 279,478 participants (42%) who were invited to participate in the survey completed the questionnaire. The participation rate was 69% in the Constances cohort, 51% in the E3NE4N cohorts and 26% in the NutriNet-Santé cohort (Fig. 1).

Table 1 presents the characteristics of included participants. Median age was 59 years old (Q1-Q3: 46 to 71 years), and 66% of the participants were women. Twenty-six percent were residents of the Ile-de-France or Grand-Est regions – the two regions with the highest rate of SARS-CoV-2 in metropolitan France, while 23% lived in rural areas and 44% lived in cities of more than 100,000 inhabitants. At least one child or adolescent was present at home in 25%. Forty-three percent were retired and 50% were working adults, but only 8% worked outside the home during the lockdown period. Ten percent of the participants were obese and a chronic disease was reported in 34% of participants.

Table 1
Participants' characteristics.

	Constances **N = 46,107**		**E3NE4N** **N = 31,398**		**Nutrinet-Santé** **N = 39,398**	**Total adults** **116,903**
		E3N N = 16,744	E4NG1 N = 4,865	E4NG2 N = 9,789		
Questionnaires First	Apr 6, 2020	Apr 17, 2020	Apr 17, 2020	Apr 9, 2020	Apr 1, 2020	Apr 1, 2020
Last	May 5, 2020	May 8, 2020	May 7, 2020	May 6, 2020	May 12, 2020	May 12, 2020
Age group (years)	9,504 (21)	0 (0)	0 (0)	764 (8)	6,296 (16)	16,564 (14)
< 40	10,483 (23)	0 (0)	0 (0)	4,016 (41)	6,701 (17)	21,200 (18)
[40–50[	9,400 (20)	0 (0)	3 (1)	3,820 (39)	7799 (20)	21,022 (18)
[50–60[	11,408 (25)	0 (0)	273 (6)	1,146 (12)	9,933 (25)	22,760 (19)
[60–70[	5,312 (16)	16,744 (100)	4,589 (94)	43 (0)	8,669 (22)	35,357 (30)
>=70						
Gender	23,426 (51)	16,744 (100)	0 (0)	6,483 (66)	30,130 (76)	76,783 (66)
Female	22,681 (49)	0 (0)	4,865 (100)	3,306 (34)	9,268 (34)	40,120 (34)
Male						
Regions	7,856 (17)	2,760 (16)	707 (15)	2,440 (25)	7,280 (18)	21,043 (18)
Ile-de-France	4,165 (9)	1,308 (8)	387 (8)	615 (6)	2,903 (7)	9,378 (8)
Grand-Est	34,086 (74)	12,673 (76)	3,770 (77)	6,218 (64)	28,086 (71)	84,833 (73)
Other French metropolitan regions	0 (0)	0 (0)	1 (0)	54 (1)	305 (1)	360 (0)
French Overseas	0	3 (0)	0 (0)	401 (4)	824 (2)	1,228 (1)
Foreign countries		0	0	61	0	61
Missing						

	Constances N = 46,107		E3NE4N N = 31,398		Nutrinet-Santé N = 39,398	Total adults 116,903
Living Area	3,349 (8)	5,125 (31)	1,613 (33)	2,784 (29)	13,550 (34)	26,421 (23)
Rural	1,310 (3)	4,526 (27)	1,454 (30)	2,330 (24)	9,174 (23)	18,794 (16)
< 20,000 inhab.	2,871 (7)	3,989 (24)	1,061 (22)	2,254 (23)	8,886 (23)	19,061 (17)
20-000-100,000 inhab.	36,473 (83)	3,005 (18)	722 (15)	2,389 (24)	7,788 (20)	50,377 (44)
> 100,000 inhab.	2,104	99	15	32	0	2,250
Missing						
Household size and composition	6,461 (14)	4,869 (30)	168 (4)	1200 (12)	7,855 (20)	20,553 (18)
Nb adults (inc. participants)	18,963 (41)	10,601 (65)	4,260 (91)	2,465 (25)	18,032 (46)	54,231 (47)
1	20,274 (44)	751 (5)	253 (5)	5,990 (61)	13,360 (34)	40,268 (35)
2	248 (1)	44 (0)	6 (0)	87 (1)	151 (0)	536 (0)
3–6	161	479	178	47	0	865
7 or +	31,462 (68)	16,089 (99)	4,640 (99)	5,033 (52)	29,841 (76)	87,908 (75)
Missing	5,637 (12)	100 (1)	33 (1)	1,852 (19)	4,063 (10)	11,693 (10)
Nb children (< 18yrs)	6,761 (15)	61 (0)	11 (0)	2,151 (22)	4,189 (11)	13,186 (11)
0	2,078 (5)	13 (0)	3 (0)	701 (7)	1,301 (3)	4,097 (4)
1	8 (0)	2 (0)	0 (0)	5 (0)	4 (0)	19 (0)
2	161	479	178	47	0	865
3–6						
7 or +						
Missing						
Educational level	5,843 (13)	971 (6)	595 (12)	9,789	5,830 (15)	13,239 (13)
<High-school degree	23,839 (53)	7,486 (46)	1,335 (28)		17,247 (44)	49,907 (47)
High-school degree or undergraduate	15,257 (34)	7,790 (48)	2,906 (60)		16,060 (41)	42,013 (40)
Graduate degree or doctorate	1,168	497	29		261	11,744
Other or Missing						

	Constances N = 46,107		E3NE4N N = 31,398		Nutrinet-Santé N = 39,398	Total adults 116,903
Professional activity before lockdown	402 (1)	6 (0)	0 (0)	19 (0)	426 (1)	853 (1)
Student	29,153 (63)	47 (0)	31 (1)	8,299 (85)	20,529 (52)	58,059 (50)
Working	1,543 (3)	1 (0)	3 (0)	336 (3)	1,128 (3)	3,111 (3)
Looking for a job	13,678 (30)	16,188 (97)	4,705 (97)	756 (8)	15,368 (39)	50,695 (43)
Retired	383 (1)	9 (0)	3 (0)	110 (1)	552 (1)	1,057 (1)
Not working due to health conditions	806 (2)	438 (3)	113 (2)	205 (2)	1295 (3)	2,857 (2)
No professional activity (housewife or husband)	142	55	10	64	0	271
Missing						
Essential job position	1,968 (4)	0 (0)	1 (0)	555 (6)	1,744 (4)	4,268 (4)
Healthcare worker	5,330 (12)	6 (0)	2 (0)	1,423 (15)	4,250 (11)	11,011 (9)
Other essential job						
Professional activity during lockdown	16,812 (36)	16,642 (100)	4824 (100)	1426 (16)	18,869 (53)	58,873 (54)
Not working	2,304 (5)	12 (0)	0 (0)	423 (5)	1,703 (5)	4,442 (4)
Stopped working	15,030 (35)	17 (0)	14 (0)	5,015 (56)	8,910 (25)	28,986 (27)
Working from home, remote working	2,908 (7)	2 (0)	5 (0)	899 (10)	2,201 (6)	6,015 (6)
Partially working from home	4,189 (10)	1 (0)	1 (0)	902 (10)	3,614 (10)	8,707 (8)
Working outside home	1,321 (3)	2 (0)	3 (0)	359 (4)	104 (0)	1,789 (2)
Other	3,543	68	18	765	3,997	8,391
Missing						

	Constances N = 46,107		E3NE4N N = 31,398		Nutrinet-Santé N = 39,398	Total adults 116,903
BMI (kg/m^2)	1,147 (2)	633 (4)	31 (1)	296 (4)	1,752 (5)	3,859 (3)
< 18.5	26,254 (58)	9,621 (59)	2,385 (49)	5,173 (63)	23,054 (60)	66,487 (59)
[18.5; 25[	13,320 (30)	4,597 (28)	2023 (42)	1,944 (24)	9,538 (25)	31,422 (28)
[25; 30[(overweight)	4,173 (9)	1,402 (9)	382 (8)	763 (9)	4,098 (11)	10,818 (10)
>=30 (obese)	1213	491	44	1613	956	3873
Missing						
Chronic diseases	11,777 (26)	7,984 (48)	2,826 (58)	2,338 (24)	14,310 (36)	39,235 (34)
Yes	33,891 (74)	8,490 (51)	1,977 (41)	7,378 (75)	24,752 (21)	76,488 (66)
No	284 (1)	195 (1)	51 (1)	65 (1)	336 (1)	931 (1)
Don’t know	155	75	11	8	0	249
Missing						
Chronic diseases	1,399 (3)	5,794 (35)	1,572 (32)	295 (3)	7,042 (18)	16,102 (14)
Asthma, COPD, other respir. diseases	690 (2)	3,252 (20)	1,127 (23)	127 (1)	1,417 (4)	6613 (6)
Diabetes	2,993 (7)	3,275 (20)	1,218 (25)	469 (5)	4,787 (12)	12,742 (11)
Hypertension	934 (2)	1,012 (6)	727 (15)	101 (1)	1,293 (3)	4,067 (3)
Other cardiovascular diseases	602 (1)	755 (5)	426 (9)	108 (1)	4,525 (11)	6,416 (6)
Cancer	1,083 (2)	619 (4)	106 (2)	267 (3)	1,323 (3)	3,398 (3)
Anxiety, depression	3,253 (7)	3,430 (21)	791 (16)	569 (6)	7,408 (19)	15,451 (13)
Other	142	55	10	64	0	249
Missing						

	Constances N = 46,107		E3NE4N N = 31,398		Nutrinet-Santé N = 39,398	Total adults 116,903
History of Acute Respiratory Infection (ARI)	3,687 (8)	1,200 (7)	312 (6)	1,018 (10)	4,139 (11)	10,356 (9)
ARI before March 1st	3,961 (9)	593 (4)	176 (4)	1,083 (11)	3,500 (9)	9,313 (8)
ARI after March 1st	691 (2)	48 (0)	12 (0)	70 (1)	203 (1)	1,024 (1)
ARI date unspecified	78	59	15	22	0	174
Missing						

Participants who were living outside mainland France (n = 1,588) or with missing information on their exact address location (n = 61) or who reported a positive SARS-CoV-2 test result (n = 342) and/or a possible COVID-19 onset (n = 8,289) before the at-risk period were excluded from the primary analysis. The primary analysis evaluated 106,848 participants: 3,035 possible COVID-19 were reported during 62,099 person-months of follow-up. The unweighted cumulative incidences of possible COVID-19 were 6.2% (95% Confidence Interval (95%CI): 5.7%; 6.6%), 7.7% (95%CI 7.3%; 8.2%) and 8.8% (95%CI 8.3%; 9.2%) on days 15, 30 and 45 of lockdown, respectively. The weighted cumulative incidences were 7.2% (95%CI 6.7%; 7.8%), 9.0% (95%CI 8.4%; 9.5%) and 10.1% (95%CI 9.6%; 10.6%) on days 15, 30 and 45 of lockdown, respectively.

Extending possible COVID-19 definition to illness that lasted less than 4 days, 5,313 cases were identified during 59,768 person-months of follow-up with unweighted cumulative incidences of 9.7% (95%CI 9.2%; 10.3%), 12.6% (95%CI 12.0%; 13.1%) and 14.3% (95%CI 13.7%;14.9%) on days 15, 30 and 45 of lockdown, respectively. Sensitivity analysis of all cases of possible COVID-19 onset after March 16, 2020 excluded 171 participants with a positive test result and/or 4,084 with the onset of possible COVID-19 before March 16, 2020 and identified 7,240 cases in 110,207 person-months of follow-up with unweighted cumulative incidences of 4.7% (95%CI 4.5%; 4.8%), 6.6% (95%CI 6.5%; 6.8%) and 7.7% (95%CI 7.5%;7.9%) on days 15, 30 and 45 of lockdown, respectively.

The primary daily incidence rate peaked on day 4 of lockdown (March 19, 2020; unweighted estimate 5.57 per 1000 person-days (95%CI 4.45; 6.89) – Fig. 2) and showed a sharp and constant decrease to reach less than 1 per 1000 person-days after day 25 (April 9, 2020). Similar findings were observed in the weighted incidence rates and the sensitivity analysis considering a different at-risk period (supplementary Figs. 1&2). Daily incidence rates were higher but showed a similar temporal pattern when the case-definition of possible COVID-19 included illness that lasted less than 4 days (supplementary Fig. 3).

Eighty out of 189 participants who experienced possible COVID-19 and were tested reported a positive (RT-PCR) test result (supplementary table 1). Headaches, rhinorrhea and fatigue were frequently reported in addition to the symptoms defining possible COVID-19. Seven-hundred and forty-nine (25%) participants

with possible COVID-19 sought medical advice and a diagnosis of COVID-19 was considered to be very likely or likely by the physician in 375 (62%) of the first 604 medical visits. Paracetamol was taken by 62% and antibiotics by 6% of participants with possible COVID-19. Only 8 participants used chloroquine or hydroxychloroquine. Forty percent participants stayed strictly confined at home following symptoms onset.

Table 2 presents the unweighted incidence rates of possible COVID-19 and the hazard ratios obtained from the univariable Cox models with stratification on source cohort. Almost all tested factors were found to be associated with possible COVID-19. A positive RT-PCR in another household member was strongly associated with possible COVID-19 in the participant; this variable was not included in the multivariable analysis to avoid overfitting. On multivariable analysis (Table 3), the risk of COVID-19 was lower in older age groups and was higher in the Ile-de-France and Grand-Est regions (compared to other French metropolitan regions), in those living in cities > 100,000 inhabitants (*vs* rural areas), when at least one child or adolescent was living in the same household, in overweight or obese participants, and in people with chronic respiratory diseases, anxiety or depression and chronic diseases other than diabetes, cancer, hypertension or other cardiovascular diseases. The observed associations were confirmed in the sensitivity analyses, except that male gender, living in a household of size 2 and being retired were negatively associated with the risk of possible COVID-19 in addition to factors identified in the primary analysis (supplementary Tables 2 & 3).

Table 2
Unweighted incidence rates of possible COVID-19 by covariate values and univariable hazard-ratios*

	Number possible COVID-19 /number person-months	Incidence rate (95%CI) (/100 person-months)	Hazard-Ratio	P-Value
Age group (years)	732/8,561	8.55 (7.94; 9.19)	Reference	0.0053
< 40	783/10,980	7.13 (6.64; 7.65)	0.87 (0.78; 0.96)	< 0.0001
[40–50[	619/10,912	5.67 (5.23; 6.14)	0.68 (0.61;0.75)	< 0.0001
[50–60[	480/12,120	3.96 (3.61; 4.33)	0.43 (0.38;0.48)	< 0.0001
[60–70[	421/19,526	2.16 (1.96; 2.37)	0.27 (0.23; 0.31)	
>=70				
Gender	1,937/40,626	4.77 (4.56;4.99)	reference	0.0011
Female	1,098/21,473	5.11 (4.82; 5.43)	0.88 (0.81; 0.95)	
Male				
Regions	697/11,081	6.29 (5.83; 6.78)	1.38 (1.27; 1.51)	< 0.0001
Ile-de-France	286/4,908	5.83 (5.17; 6.54)	1.30 (1.15; 1.48)	< 0.0001
Grand-Est	2,052/46,110	4.45 (4.26; 4.65)	reference	
Other French metropolitan regions				
Living Area	539/14,249	3.78 (3.47; 4.12)	Reference	0.2903
Rural	386/10,069	3.83 (3.46; 4.24)	1.07 (0.94; 1.22)	0.0010
< 20,000 inhab.	465/10,114	4.60 (4.19; 5.04)	1.23 (1.09; 1.40)	< 0.0001
20-000-100,000	1,581/26,458	5.98 (5.68; 6.28)	1.26 (1.12; 1.41)	
> 100,000 inhab.	64/1,209	5.29 (4.08; 6.76)		
Missing				

* with stratification on cohort study.

	Number possible COVID-19 /number person-months	Incidence rate (95%CI) (/100 person-months)	Hazard-Ratio	P-Value
Household size and composition	495/10,881	4.55 (4.16; 4.97)	Reference	0.0002
1	1,076/29,241	3.68 (3.46; 3.91)	0.81 (0.73; 0.91)	< 0.0001
2	1,453/21,496	6.76 (6.42; 7.12)	1.36 (1.23; 1.51)	< 0.0001
3 or +	11/481	2.29 (1.14; 4.09)	Reference	
Missing	1,881/46,600	4.04 (3.86; 4.22)	1.77 (1.64; 1.91)	
Children (< 18yrs)	1,143/15,018	7.61 (7.18; 8.07)		
0	11/481	2.29 (1.14; 4.09)		
1 or +				
Missing				
Educational level	275/7,178	3.83 (3.39; 4.31)	Reference	< 0.0001
<High-school degree	1,311/26,739	4.90 (4.64; 5.18)	1.35 (1.19; 1.54)	< 0.0001
High-school degree or undergraduate	1,147/22,155	5.18 (4.88; 5.49)	1.56 (1.37; 1.78)	
Graduate degree or doctorate	302/6,027	5.01 (4.46; 5.61)		
Missing				

* with stratification on cohort study.

	Number possible COVID-19 /number person-months	Incidence rate (95%CI) (/100 person-months)	Hazard-Ratio	P-Value
Professional activity before lockdown	36/446	8.07 (5.65; 11.2)	1.18 (0.85; 1.64)	0.3221
Student	2,025/30,170	6.71 (6.42; 7.01)	Reference	0.8955
Working	113/1,578	7.16 (5.90; 8.61)	1.01 (0.84; 1.22)	< 0.0001
Looking for a job	740/27,739	2.67 (2.48; 2.87)	0.43 (0.39; 0.47)	0.0415
Retired	48/529	9.07 (6.69; 12.0)	1.35 (1.01; 1.79)	0.0006
Not working due to health conditions	62/1,490	4.16 (3.19; 5.33)	0.64 (0.50; 0.83)	
No professional activity (housewife or husband)	11/147	7.50 (3.74; 13.4)		
Missing				
Essential job position	161/2,207	7.29 (6.21; 8.51)	1.44 (1.23; 1.69)	< 0.0001
Healthcare worker (Y *vs* N)	361/5,750	6.28 (5.65; 6.96)	1.20 (1.08; 1.35)	0.0010
Other essential job (Y *vs* N)				
Professional activity during lockdown	999/31,782	3.14 (2.95; 3.34)	0.56 (0.51; 0.62)	< 0.0001
Not working	173/2,321	7.45 (6.38; 8.65)	1.12 (0.95; 1.32)	0.1691
Stopped working	959/15,052	6.37 (5.97; 6.79)	Reference	0.7257
Working from home, remote working	188/3,143	5.98 (5.16; 6.90)	0.97 (0.83; 1.14)	0.0835
Partially working from home	313/4,573	6.84 (6.11; 7.65)	1.12 (0.99; 1.27)	0.6136
Working outside home	68/951	7.15 (5.55; 9.07)	1.07 (0.83; 1.36)	
Other	335/4,277	7.83 (7.02; 8.72)		
Missing				

* with stratification on cohort study.

	Number possible COVID-19 /number person-months	Incidence rate (95%CI) (/100 person-months)	Hazard-Ratio	P-Value
BMI (kg/m^2)	104/2,035	5.11 (4.18; 6.19)	1.15 (0.94; 1.40)	0.1746
< 18.5	1,621/35,552	4.56 (4.34; 4.79)	Reference	0.0763
[18.5; 25[	826/16,650	4.96 (4.63; 5.31)	1.08 (0.99; 1.17)	< 0.0001
[25; 30[(overweight)	365/5,615	6.50 (5.85; 7.20)	1.40 (1.25; 1.56)	
>=30 (obese)	119/2,247	5.30 (4.39; 6.34)		
Missing				
Chronic diseases	1,005/20,670	4.86 (4.57; 5.17)	1.12 (1.03; 1.21)	0.0053
Yes	1,993/40,834	4.88 (4.67; 5.10)	Reference	0.0015
No	34/461	7.38 (5.11; 10.3)	1.73 (1.23; 2.43)	
Didn’t know	3/135	2.23 (0.46; 6.51)		
Missing				
Chronic diseases (Y *vs* N)	415/8,319	4.99 (4.52; 5.49)	1.51 (1.35; 1.69)	< 0.0001
Asthma, COPD, other resp. diseases	113/3,582	3.15 (2.60; 3.79)	1.00 (0.83; 1.22)	0.9662
Diabetes	270/6,780	3.98 (3.52; 4.49)	0.92 (0.81; 1.04)	0.1682
Hypertension	79/2,194	3.60 (2.85; 4.49)	0.88 (0.70; 1.10)	0.2493
Other cardiovascular diseases	168/3,286	5.11 (4.37; 5.95)	1.14 (0.97; 1.34)	0.1078
Cancer	132/1,702	7.75 (6.49; 9.20)	1.72 (1.44; 2.04)	< 0.0001
Anxiety, depression	432/8,003	5.40 (4.90; 5.93)	1.27 (1.15; 1.41)	< 0.0001
Other	3/135	2.23 (0.46;6.51)		
Missing				

* with stratification on cohort study.

	Number possible COVID-19 /number person-months	Incidence rate (95%CI) (/100 person-months)	Hazard-Ratio	P-Value
Positive RT-PCR in another household member (Y *vs* N)	58/207	28.0 (21.2; 36.1)	5.68 (4.38; 7.37)	< 0.0001

* with stratification on cohort study.

Table 3
Multivariable-adjusted hazard-ratios of possible COVID-19 according to covariate values*.

	Hazard-Ratio	P-Value
Age group	Reference	< 0.0001
< 40	0.80 (0.72; 0.90)	< 0.0001
[40–50[	0.68 (0.60;0.76)	< 0.0001
[50–60[	0.52 (0.44;0.62)	< 0.0001
[60–70[	0.34 (0.27; 0.44)	
>=70		
Gender	reference	0.7267
Female	0.99 (0.91; 1.07)	
Male		
Regions	1.31 (1.19; 1.44)	< 0.0001
Ile-de-France	1.29 (1.14; 1.47)	< 0.0001
Grand-Est	reference	
Other French metropolitan regions		
Living Area	Reference	0.3629
Rural	1.07 (0.93; 1.22)	0.0471
< 20,000 inhab.	1.14 (1.00; 1.30)	0.0241
20-000-100,000 inhab.	1.15 (1.02; 1.29)	
> 100,000 inhab.		

* with stratification on the cohort. 6,567 (6%) participants excluded from the multivariable model due to missing values including 190 with possible COVID-19; educational level was not significantly associated with possible COVID-19 when included in the multivariable model (high school degree or undergraduate versus < high-school degree, P = 0.7743; graduate or doctorate versus < high-school degree, P = 0.6299), and was not kept in the final model due to missing information on this covariate in the E4NG2 cohort. To avoid overfitting Positive RT-PCR in another household member was not entered in the model. However, results were unchanged when this variable was entered (not shown).

	Hazard-Ratio	P-Value
Household size and composition	Reference	0.3405
1	0.95 (0.85; 1.06)	0.9603
2	1.00 (0.87; 1.16)	0.0001
3 or +	Reference	
Children (< 18yrs)	1.28 (1.13; 1.45)	
0		
1 or +		
BMI (kg/m2)	1.04 (0.85; 1.27)	0.6916
< 18.5	Reference	0.0005
[18.5; 25[	1.17 (1.07; 1.27)	< 0.0001
[25; 30[(overweight)	1.41 (1.25; 1.58)	
>=30 (obese)		
Professional activity before lockdown	1.01 (0.71; 1.44)	0.9620
Student	Reference	0.6618
Working	1.05 (0.86; 1.27)	0.1057
Looking for a job	0.86 (0.72; 1.03)	0.0894
Retired	1.30 (0.96; 1.77)	0.3773
Not working due to health conditions	0.89 (0.68; 1.16)	
No professional activity (house wife or husband)		
Essential job position	1.18 (1.00; 1.40)	0.0535
Health care worker (Y *vs* N)	1.01 (0.90; 1.14)	0.8922
Other essential job (Y *vs* N)		

* with stratification on the cohort. 6,567 (6%) participants excluded from the multivariable model due to missing values including 190 with possible COVID-19; educational level was not significantly associated with possible COVID-19 when included in the multivariable model (high school degree or undergraduate versus < high-school degree, P = 0.7743; graduate or doctorate versus < high-school degree, P = 0.6299), and was not kept in the final model due to missing information on this covariate in the E4NG2 cohort. To avoid overfitting Positive RT-PCR in another household member was not entered in the model. However, results were unchanged when this variable was entered (not shown).

	Hazard-Ratio	P-Value
Chronic diseases (Y vs N)	1.41 (1.24; 1.60)	< 0.0001
Asthma, COPD, other resp. diseases	1.31 (1.08; 1.58)	0.0065
Anxiety, depression	1.22 (1.08; 1.37)	0.0013
Other		

* with stratification on the cohort. 6,567 (6%) participants excluded from the multivariable model due to missing values including 190 with possible COVID-19; educational level was not significantly associated with possible COVID-19 when included in the multivariable model (high school degree or undergraduate versus < high-school degree, P = 0.7743; graduate or doctorate versus < high-school degree, P = 0.6299), and was not kept in the final model due to missing information on this covariate in the E4NG2 cohort. To avoid overfitting Positive RT-PCR in another household member was not entered in the model. However, results were unchanged when this variable was entered (not shown).

Discussion

Lockdown was associated with a strong decrease in the incidence of possible COVID-19 in the French adult population that participated in this survey. This study shows that the cumulative incidence of possible COVID-19 on day 45 of lockdown ranged from 7.7–10.2% depending on the estimation method, that more than sixty percent of new cases occurred within the first two weeks, and that the daily incidence remained at a sustained low level 1 month after lockdown and thereafter. In addition, we identified several risk factors of possible COVID-19 during this period, and have described the immediate consequences in terms of access to healthcare and treatment associated with these syndromes. To our knowledge this is the first study to report the signs and symptoms of COVID-19 on a nationwide scale and during lockdown.

Considering the estimated 5-day median incubation time of COVID-19 and the appearance of symptoms within 12 days after infection,[9] a large proportion of participants who developed possible COVID-19 in the first two weeks were probably infected before lockdown, most of them in the community or at the workplace. It is therefore not surprising to find the association of mild-to-moderate possible COVID-19 in adults with decreasing age,[10] living in urban versus rural environments,[11] in highly prevalent French regions,[12] who are healthcare professionals,[13] all factors that were reported in other studies performed before lockdown. We also identified factors indicating potential secondary household-related transmission,[14] such as living with children or another person with a positive diagnosis of SARS-CoV-2. However, it was impossible to determine a timeframe for the latter factor and identify whether the participant was the source of infection or was infected by a household member. Obesity has been found to be linked with the risk of severe possible COVID-19 in young patients,[15] and also suspected to increase the susceptibility to infection.[16] Different theories suggest that asthma, COPD and other respiratory diseases may be negatively or positively associated with the susceptibility to SARS-CoV-2 infection due to up or down regulation of angiotensin-converting enzyme-2 expression. However, all of these respiratory diseases have been shown to be associated with the severity of illness in infected persons.[17–19] Since

30–60% of SARS-CoV-2 infections are asymptomatic[20–23] and were not included in our possible COVID-19 cases, by definition, it is not surprising to find the presence of these conditions, which are known to be associated with more severe disease, in subjects with symptomatic SARS-CoV-2 infection.

Our study has several limitations. The most important limitation is the lack of virological confirmation of possible COVID-19 and the risk of misclassification of a SARS-CoV-2 infection and a disease from another etiology. During lockdown, French health authority recommendations limited SARS-CoV-2 testing with a RT-PCR test to patients with severe symptoms requiring hospitalization or to specific situations (e.g. healthcare workers with symptoms). Thus, testing was not available to most participants. Nevertheless, the influenza season peaked on week 6 and ended on week 10 to 12, just before lockdown, which limits the risk of acute respiratory infection caused by an influenza virus. In addition, 42% of the small group of participants who were tested for SARS-CoV-2 infection in our study reported a positive RT-PCR result. This positive rate was higher than that reported in the community (30% at its highest between March 23 and March 29, 2020).[24] However, a 15–20% seroprevalence of SARS-CoV-2 was reported in Spain in individuals from the general population who presented symptoms compatible with COVID-19.[23] It is therefore likely that the cause of illness was not SARS-CoV-2 infection in a significant proportion of our possible COVID-19 cases and only studies using sensitive and specific virological methods can accurately quantify the extent of the SARS-CoV-2 epidemic. To avoid recall bias, which is another potential limitation of our study, we limited the questionnaire to the symptoms present in the past 14 days. Finally, although participation bias was accounted for with an appropriate weighting method, our findings should not be considered to be strictly representative of the general adult population in France. Nevertheless, the large number of subjects from all social categories allows us to draw robust conclusions on the factors associated with the occurrence of possible COVID-19 in France.

Conclusion

In conclusion, to our knowledge this is the first study to quantify the incidence of possible COVID-19 in the general population on a nationwide scale and during a lockdown, and it shows the significant impact of lockdown on the dynamics of the incidence of infection. A follow-up study is ongoing and will be combined with SARS-CoV-2 serological tests of all participants to estimate the seroprevalence and identify the associated factors.

Strengths And Limitations Of This Study

- Lockdown was associated with a strong decrease in the incidence of possible COVID-19 in the French adult population.
- We identified several risk factors of possible COVID-19 during this period, and we described the immediate consequences in terms of access to healthcare and treatment.
- The most important limitation was the lack of virological confirmation of possible COVID-19 and the risk of misclassification of a SARS-CoV-2 infection and a disease from another etiology.

- Although participation bias was accounted for with an appropriate weighting method, our findings should not be considered to be strictly representative of the general adult population in France

Abbreviations

OR: Odds-Ratio, CI: Confidence Intervals

Declarations

Ethics approval and consent to participate

Ethical approval and written informed consent was obtained from each participant before enrolment in the original cohort. The study was approved by the Inserm ethics evaluation committee (approval #20-672 dated March 30, 2020). According to French law, the present nested survey did not require specific additional written consent from the participant. Representatives of the participants tested and validated the questionnaires, but they did not contribute to other aspects related to the design, conduct, reporting or dissemination of the research.

Avaibility of data and materials

In regards to data availability, data of the study are protected under the protection of health data regulation set by the French National Commission on Informatics and Liberty (Commission Nationale de l'Informatique et des Libertés, CNIL). The data can be available upon reasonable request to the corresponding author (fabrice.carrat@iplesp.upmc.fr), after a consultation with the steering committee of the Sapris study. The French law forbids us to provide free access to Sapris data; access could however be given by the steering committee after legal verification of the use of the data.

Competing interests

Prof Fabrice Carrat, Mathilde Touvier, Prof Gianluca Severi, Prof Laurence Meyer, Prof Florence Jusot, Nathanael Lapidus, Delphine Rahib, Nathalie Lydié, Marie-Aline Charles, Prof Pierre-Yves Ancel, Alexandra Rouquette, Claude Martin, Prof Xavier de Lamballerie, Prof Marie Zins, Nathalie Bajos declare no competing interest.

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Role of the funding source

Sponsor and funding sources played no role in the study design, data collection, analysis, interpretation or drafting of the study. FC had full access to all data in the study and FC and NB made the final decision to submit the study for publication.

This study

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Authors' Contribution.

Study idea and design: Carrat, Touvier, Severi, Meyer, Jusot, Charles, Ancel, Zins, Bajos.

Data acquisition: Touvier, Severi, Zins.

Data analysis and interpretation: Carrat, Touvier, Severi, Meyer, Jusot, Zins, Bajos

Drafting of the manuscript: Carrat

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Carrat, Lapidus

Obtained funding: Carrat, Bajos

Administrative, technical, or material support: Rahib, Lydié

Study supervision: Carrat, Touvier, Severi, Charles, Ancel, de Lamballerie, Zins, Bajos

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