

# An assessment of case-fatality and infection-fatality rates of first and second COVID-19 waves in Italy

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**Abstract.** *Background and aim:* The exact COVID-19 severity is still not well defined and it is hotly debated due to a few methodological issues such as the uncertainties about the spread of the SARS-CoV-2 infection. *Methods:* We investigated COVID-19 case-fatality rate and infection-fatality rate in 2020 in Italy, a country severely affected by the pandemic, basing our assessment on publicly available data, and calculating such measures during the first and second waves. *Results:* We found that province-specific crude case-fatality rate in the first wave (February-July 2020) had a median value of 12.0%. Data about infection-fatality rate was more difficult to compute, due to large underestimation of SARS-CoV-2 infection during the first wave when asymptomatic individuals were very rarely tested. However, when using reference population-based seroprevalence data for anti-SARS-CoV-2 antibodies collected in May-July 2020, we computed an infection-fatality rate of 2.2%. During the second wave (Sep-Dec 2020), when SARS-CoV-2 testing was greatly increased and extended to many asymptomatic individuals, we could only compute a 'hybrid' case/infection-fatality rate with a value of 2.2%, similar to the infection-fatality rate of the first wave. *Conclusions:* Overall, this study allowed to assess the COVID-19 case- and infection-fatality rates in Italy before of variant spread and vaccine availability, confirming their high values compared with other airborne infections like influenza. Our findings for Italy were similar to those characterizing other Western European countries.

**Key words:** COVID-19, case-fatality rate, epidemiology, infection-fatality rate, outbreak, public health, SARS-CoV-2, seroprevalence, wave

## Introduction

The COVID-19 pandemic is one of the greatest medical challenges of the last century (1), especially for the possible clinical presentation as a severe and life-threatening disease (2), with limited therapeutic options, and long-term sequelae (3-5). Since the beginning, attempts to control the pandemic spread relied on public health measures such as social distancing, contact tracing, use of face masks and other protective gears (like goggles or face shields in health

care settings), and lockdowns with limitations of population mobility (6-10). Still in recent months that vaccines are available, the presence of virus variants and the possibility of reinfection are of great concern (11-13).

Italy was the first Western country severely hit by the pandemic, with a widespread population involvement, especially in the North of the country during the first wave (14). Factors associated with increased susceptibility to COVID-19 onset and severity, following the infection with SARS-CoV-2, have been

shown to be male sex, and presence of a comorbidity such as hypertension, diabetes, cardiovascular disease, or chronic lung disease (15,16). Also, environmental factors may play a role increasing COVID-19 susceptibility and severity (17-21) as also reported in previous studies carried out in Northern Italy suggesting a positive association between air pollutant levels with both SARS-CoV-2 incidence and COVID-19 mortality (22-24).

During the 2020, Italy experienced two pandemic waves. The first wave started with the first diagnosed case on February 20, 2020 and lasted till end of June 2020, leading to the implementation of a tight lockdown from March 8 to May 4, 2020 (6). After a brief summer period characterized by light restrictions due to the very low number of newly diagnosed cases, from September 2020 cases rapidly increased again, leading to a second, lighter lockdown from November 6, 2020 (25). Since begin of the vaccination campaign in a few subjects in December 27, 2020 and during the 2021, Italy has experienced a subsequent third wave in February-May 2021 and a fourth one in the most recent period, although the last ones have been largely mitigated by the growing number of vaccinated people (26).

Due to lack of a large availability of SARS-CoV-2 swab tests during the first wave, SARS-CoV-2 infection testing was limited to subjects with symptoms potentially related to COVID-19 as well to health professionals (27-29). From the end of the first lockdown, availability of SARS-CoV-2 swab tests greatly increased and, therefore, testing has been extended to asymptomatic and pauci-symptomatic subjects (30). In particular, drive-through facilities have been implemented in several Italian cities with up to 1000 daily tests (31). For this reason, number of SARS-CoV-2 infections was certainly underestimated during the first wave (14), as also confirmed by the nationwide seroprevalence data made available by the National Institute of Statistics based on a population-based survey conducted in May-July 2020 (32). As consequence, there are uncertainties and controversies about the severity of COVID-19 and namely its case-fatality rate (number of COVID-19 deaths divided by COVID-19 cases, i.e. the symptomatic subjects diagnosed with the disease) and infection-fatality rate (number of deaths divided by overall number of cases of SARS-CoV-2 infection, i.e. including both symptomatic and

asymptomatic subjects), due to methodological issues (33). Such issues include the censoring when the outcome is still unknown at the time of the investigation, the occurrence of ascertainment biases (34-36), especially the underestimation SARS-CoV-2 infection and COVID-19 incidence during an emergency situation as during the pandemic spread, and heterogeneity in classifying the outcome, i.e. COVID-19 related deaths (37-41).

In this study, we aimed at assessing COVID-19 fatality rates in Italy, focusing on case-fatality and infection-fatality rates during the first and second waves on a provincial level during the first year of the COVID-19 pandemic, when neither virus variants were present in the country nor the vaccination campaign had started yet (42,43).

## Methods

We downloaded publicly available COVID-19 data from the website of the Civil Protection Agency (44) and National Institute of Statistics (45), collecting daily data flow that Italian regions had to mandatorily provide with a provincial level of detail. In detail, we used the number of newly diagnosed infections with SARS-CoV-2 (corresponding to the new positive tests of infection based on quantitative reverse transcription polymerase chain reaction) and number of COVID-19 deaths in two time frames: from February 24-June 30, 2020 (first wave), and from September 1-December 31, 2020 (second wave). We also used data about anti-SARS-CoV-2 antibody seroprevalence recently made available at a provincial level by a survey carried out by the National Institute of Statistics in May-July 2020 (32). In order to take into account possible differences in time-frame between the first wave period and the seroprevalence survey, we also considered as alternative first wave period February 24-July 31, 2020.

We calculated the province-specific case-fatality rate, also called ratio (34,46), for the first and second waves by dividing the number of deaths by the number of diagnosed positive cases in the two periods February 24-June 30 and February 24-July 31, 2020. We then calculated the province-specific infection-fatality rate (34) by dividing the number of deaths occurred during the first wave (February 24-June 30, 2020) by the

estimated number of seroprevalent subjects using data of the National Institute of Statistics carried out in the period May–July 2020 (32). We eventually computed the rate between deaths and positive molecular tests during the September 1–December 31 period, that we called ‘case/infection-fatality rate’ due to the hybrid nature of such indicator, whose denominator included asymptomatic and symptomatic SARS-CoV-2 infected cases due to nationwide marked changes in testing availability and policy (14). All these estimates were crude, i.e. unadjusted for age and sex.

Using data made publicly available by the European Center for Disease Control (ECDC), we also retrieved COVID-19 cases and deaths occurred in all European countries during the 2020, available on a weekly basis (47). As we did with Italian provinces, we calculated the case-fatality rate and the case/infection-fatality rate for the first and second waves, respectively. For this purpose, we considered as first wave the time from the beginning of the virus spread up to summer period (June 30, 2020) when cases waned in almost all countries (some countries experienced a unique wave in the 2020). The beginning of second wave was considered variable according to the raising of the curve up to the end of the year, generally January 1, 2021 based on the weekly availability of data (47).

We also compared data of fatality rate of COVID-19 with seasonal flu. We retrieved data of flu cases through reports released by the National Institute of Health (48), while we used annual flu deaths available

from the National Institute of Statistics (49). We excluded the most recent years, taking into account the influence of the COVID-19 pandemic in the circulation of other airborne infections (50).

To investigate the relation between province-specific estimates, we used linear regression to fit a restricted cubic spline model with three knots at fixed percentiles (10th, 50th and 90th) of first wave distribution and weighted by the provincial population in 2020 (51). We used a multivariable model adjusted for aging index, percentage commuting outside the municipality of residence on a daily basis, and percentage of dwellings occupied by only one resident, available using 2011 census data of the National Institute of Statistics (51). We used the Stata statistical software (Version-17.0 Stata Corp., College Station-TX, 2021) for all analyses.

## Results

Table 1 presents detailed information about number of cases and deaths divided by first and second waves along with seroprevalence data in the Italian provinces. In Italy, diagnosed cases and deaths during the first wave were 235,839 and 35,048, respectively. Corresponding values for the second wave were 1,808,260 cases and 40,392 deaths.

National average seroprevalence was 2.49%, with the highest values in Bergamo (24.3%), Cremona

**Table 1.** Number of SARS-CoV-2 cases, COVID-19 deaths, COVID-19 case-fatality rate (deaths/cases\*100) in the first (1st) wave (February 24–June 30), and case/infection-fatality rate (deaths/cases\*100) in the second (2nd) waves (September 30–December 31) in 2020 divided by province and region. SARS-CoV-2 seroprevalence (%) after the 1st wave (period May–July 2020) and infection-fatality rate (deaths/seroprevalents\*100).

Region/ Province	Population Jan 1, 2020	Cases 1 <sup>st</sup> wave	Cases 2 <sup>nd</sup> wave	Seroprev. (%)	Deaths 1 <sup>st</sup> wave	Deaths 2 <sup>nd</sup> wave	Case- fatality rate 1 <sup>st</sup> wave	Infection- fatality rate 1 <sup>st</sup> wave	Case/ infection fatality rate 2 <sup>nd</sup> wave
<b>Aosta Valley</b>	<b>125501</b>	<b>1195</b>	<b>5771</b>	<b>3.72</b>	<b>145</b>	<b>239</b>	<b>12.1</b>	<b>3.1</b>	<b>4.1</b>
Aosta	125501	1195	5771	3.72	145	239	12.1	3.1	4.1
<b>Lombardy</b>	<b>10103969</b>	<b>91813</b>	<b>368273</b>	<b>7.35</b>	<b>16633</b>	<b>8321</b>	<b>18.1</b>	<b>2.2</b>	<b>2.3</b>
Bergamo	1116384	14375	12873	24.3	3137	193	21.8	1.2	1.5
Brescia	1268455	15626	25468	7.63	2686	422	17.2	2.8	1.7
Como	603828	4093	29531	2.00	587	794	14.3	4.8	2.7
Cremona	358347	6612	7664	19.7	1130	123	17.1	1.6	1.6
Lecco	337087	2831	10303	6.66	481	236	17.0	2.1	2.3

Table 1 (Continued)

Region/ Province	Population Jan 1, 2020	Cases 1 <sup>st</sup> wave	Cases 2 <sup>nd</sup> wave	Seroprev. (%)	Deaths 1 <sup>st</sup> wave	Deaths 2 <sup>nd</sup> wave	Case- fatality rate 1 <sup>st</sup> wave	Infection- fatality rate 1 <sup>st</sup> wave	Case/ infection fatality rate 2 <sup>nd</sup> wave
Lodi	230607	3570	6936	7.10	679	140	19.0	4.1	2.0
Mantua	411062	3496	12260	6.57	684	288	19.6	2.5	2.3
Milan	3279944	24379	147720	3.95	4252	3197	17.4	3.3	2.2
Monza/Brianza	878267	5772	42090	4.52	979	895	17.0	2.5	2.1
Pavia	546515	5568	18869	5.95	1241	543	22.3	3.7	2.9
Sondrio	180941	1584	6954	5.30	212	201	13.4	2.2	2.9
Varese	892532	3907	47605	1.71	565	1289	14.5	3.7	2.7
<b>Veneto</b>	<b>4907704</b>	<b>18937</b>	<b>227276</b>	<b>1.92</b>	<b>2028</b>	<b>4960</b>	<b>10.7</b>	<b>2.1</b>	<b>2.2</b>
Belluno	201972	1191	13369	1.88	114	330	9.6	3.0	2.5
Padua	939672	3954	41651	2.32	318	608	8.0	1.5	1.5
Rovigo	233386	444	6932	2.39	36	204	8.1	0.6	2.9
Treviso	888309	2673	45715	1.89	322	783	12.0	1.9	1.7
Venice	851663	2682	35612	1.68	299	863	11.1	2.1	2.4
Verona	930339	5127	44073	2.23	586	1195	11.4	2.8	2.7
Vicenza	862363	2866	39924	1.33	353	977	12.3	3.1	2.4
<b>Emilia- Romagna</b>	<b>4467118</b>	<b>28061</b>	<b>137052</b>	<b>2.90</b>	<b>4353</b>	<b>3431</b>	<b>15.5</b>	<b>3.4</b>	<b>2.5</b>
Bologna	1017806	5229	32314	2.33	732	936	14.0	3.0	2.9
Ferrara	344840	1044	7886	0.72	173	222	16.6	7.0	2.8
Forli-Cesena	394833	1740	10213	1.04	196	164	11.3	4.8	1.6
Modena	707292	3873	25945	1.10	480	601	12.4	6.2	2.3
Parma	453930	3657	8701	5.84	901	215	24.6	3.4	2.5
Piacenza	287236	4428	10187	9.54	956	252	21.6	3.5	2.5
Ravenna	389634	1030	11337	1.18	81	430	7.9	1.8	3.8
Reggio nell'Emilia	531751	4913	18248	4.45	581	306	11.8	2.5	1.7
Rimini	339796	2147	12221	2.79	253	305	11.8	2.9	2.5
<b>Piedmont</b>	<b>4341375</b>	<b>30989</b>	<b>162730</b>	<b>3.45</b>	<b>4029</b>	<b>3537</b>	<b>13.0</b>	<b>2.7</b>	<b>2.2</b>
Alessandria	419037	4063	13240	2.08	659	470	16.2	7.7	3.5
Asti	213216	1874	7960	2.13	249	217	13.3	5.5	2.7
Biella	174384	1046	5748	6.59	194	112	18.5	1.7	1.9
Cuneo	586568	2862	24081	0.87	373	494	13.0	7.3	2.1
Novara	368040	2792	12443	5.21	367	272	13.1	1.9	2.2
Turin	2252379	15889	87788	3.58	1844	1712	11.6	2.3	2.0
Verbano- Cusio-Ossola	157455	1140	5515	9.05	132	122	11.6	0.9	2.2
Vercelli	170296	1323	5955	3.52	211	138	15.9	3.5	2.3
<b>Trentino- South Tyrol</b>	<b>1074819</b>	<b>7502</b>	<b>43303</b>	<b>3.19</b>	<b>693</b>	<b>1041</b>	<b>9.2</b>	<b>2.0</b>	<b>2.4</b>

Region/ Province	Population Jan 1, 2020	Cases 1 <sup>st</sup> wave	Cases 2 <sup>nd</sup> wave	Seroprev. (%)	Deaths 1 <sup>st</sup> wave	Deaths 2 <sup>nd</sup> wave	Case- fatality rate 1 <sup>st</sup> wave	Infection- fatality rate 1 <sup>st</sup> wave	Case/ infection fatality rate 2 <sup>nd</sup> wave
Bolzano	532080	2639	26559	2.95	288	504	10.9	1.8	1.9
Trento	542739	4863	16744	3.42	405	537	8.3	2.2	3.2
<b>Friuli-Venezia Giulia</b>	<b>1211357</b>	<b>3308</b>	<b>45651</b>	<b>1.02</b>	<b>362</b>	<b>1426</b>	<b>10.9</b>	<b>2.9</b>	<b>3.1</b>
Gorizia	139206	216	5904	0.12	5	104	2.3	- <sup>†</sup>	1.8
Pordenone	312619	702	9792	1.88	68	291	9.7	1.2	3.0
Trieste	233276	1393	9107	0.59	209	270	15.0	- <sup>†</sup>	3.0
Udine	526256	997	20848	0.93	80	761	8.0	1.6	3.7
<b>Liguria</b>	<b>1543127</b>	<b>9473</b>	<b>46958</b>	<b>3.24</b>	<b>1563</b>	<b>1276</b>	<b>16.5</b>	<b>3.1</b>	<b>2.7</b>
Genoa	835829	5573	29304	3.61	943	853	16.9	3.1	2.9
Imperia	213919	1494	4806	2.39	231	79	15.5	4.5	1.6
La Spezia	219196	860	7142	1.89	159	189	18.5	3.8	2.6
Savona	274183	1546	5706	3.83	230	155	14.9	2.2	2.7
<b>Tuscany</b>	<b>3722729</b>	<b>9779</b>	<b>108429</b>	<b>0.90</b>	<b>1088</b>	<b>2491</b>	<b>11.1</b>	<b>3.3</b>	<b>2.3</b>
Arezzo	341766	676	9779	1.23	47	168	7.0	1.1	1.7
Florence	1004298	3192	29864	0.53	401	839	12.6	7.5	2.8
Grosseto	220785	396	3708	1.18	28	73	7.1	1.1	2.0
Livorno	333509	477	8079	0.56	62	195	13.0	3.3	2.4
Lucca	388678	1351	11010	0.42	151	192	11.2	9.3	1.7
Massa and Carrara	193934	1051	6442	0.00	153	179	14.6	- <sup>‡</sup>	2.8
Pisa	422310	930	15667	1.55	91	341	9.8	1.4	2.2
Pistoia	293059	747	9640	0.96	76	199	10.2	2.7	2.1
Prato	258152	532	9790	1.02	47	203	8.8	1.8	2.1
Siena	266238	427	4450	2.17	32	102	7.5	0.6	2.3
<b>Umbria</b>	<b>880285</b>	<b>1385</b>	<b>26064</b>	<b>0.67</b>	<b>80</b>	<b>530</b>	<b>5.8</b>	<b>1.4</b>	<b>2.0</b>
Perugia	655403	1008	19843	0.71	51	369	5.1	1.1	1.9
Terni	224882	377	6221	0.55	29	161	7.7	2.4	2.6
<b>Marches</b>	<b>1518400</b>	<b>6549</b>	<b>33194</b>	<b>2.59</b>	<b>987</b>	<b>720</b>	<b>15.1</b>	<b>2.5</b>	<b>2.2</b>
Ancona	469750	1875	9711	2.16	218	185	11.6	2.1	1.9
Ascoli Piceno	206363	290	4790	4.95	12	125	4.1	0.1	2.6
Fermo	173004	473	4337	2.16	67	69	14.2	1.0	1.6
Macerata	312146	1154	7851	2.16	145	159	12.6	2.2	2.0
Pesaro and Urbino	357137	2757	6505	4.95	545	182	19.8	3.1	2.8
<b>Lazio</b>	<b>5865544</b>	<b>8010</b>	<b>148533</b>	<b>1.00</b>	<b>863</b>	<b>2815</b>	<b>10.8</b>	<b>1.4</b>	<b>1.9</b>
Frosinone	485241	663	12990	0.19	79	162	11.9	8.6	1.2
Latina	576655	607	13625	0.50	44	294	7.2	1.5	2.2
Rieti	154232	411	4565	3.00	41	149	10.0	0.9	3.3

Table 1 (Continued)

Region/ Province	Population Jan 1, 2020	Cases 1 <sup>st</sup> wave	Cases 2 <sup>nd</sup> wave	Seroprev. (%)	Deaths 1 <sup>st</sup> wave	Deaths 2 <sup>nd</sup> wave	Case- fatality rate 1 <sup>st</sup> wave	Infection- fatality rate 1 <sup>st</sup> wave	Case/ infection fatality rate 2 <sup>nd</sup> wave
Rome	4333274	5872	108988	1.05	672	2016	11.4	1.4	1.8
Viterbo	316142	457	8365	1.52	27	194	5.9	0.6	2.3
<b>Abruzzo</b>	<b>1305770</b>	<b>3261</b>	<b>31124</b>	<b>1.29</b>	<b>461</b>	<b>794</b>	<b>14.1</b>	<b>2.7</b>	<b>2.6</b>
Chieti	383189	818	6284	1.40	131	136	16.0	2.4	2.2
L'Aquila	296491	225	10604	0.54	11	350	4.9	0.7	3.3
Pescara	318678	1586	5447	1.69	239	116	15.1	4.4	2.1
Teramo	307412	632	8789	1.48	80	192	12.7	1.8	2.2
<b>Molise</b>	<b>302265</b>	<b>426</b>	<b>5971</b>	<b>0.81</b>	<b>28</b>	<b>175</b>	<b>6.6</b>	<b>1.1</b>	<b>2.9</b>
Campobasso	218679	364	3829	0.66	22	110	6.0	1.4	2.9
Isernia	83586	62	2142	1.19	6	65	9.7	0.6	3.0
<b>Campania</b>	<b>5785861</b>	<b>4648</b>	<b>182462</b>	<b>0.89</b>	<b>517</b>	<b>2915</b>	<b>11.1</b>	<b>1.0</b>	<b>1.6</b>
Avellino	413926	552	8289	0.00	62	143	11.2	- <sup>‡</sup>	1.7
Benevento	274080	209	4423	0.00	19	137	9.1	- <sup>‡</sup>	3.1
Caserta	922171	543	33741	1.48	53	540	9.8	0.4	1.6
Naples	3082905	2652	111294	1.04	314	1811	11.8	1.0	1.6
Salerno	1092779	692	24715	0.31	69	284	10.0	2.1	1.1
<b>Apulia</b>	<b>4008296</b>	<b>4502</b>	<b>84951</b>	<b>0.88</b>	<b>566</b>	<b>2037</b>	<b>12.6</b>	<b>1.6</b>	<b>2.4</b>
Bari	1249246	1491	33237	1.50	153	636	10.3	0.8	1.9
Barletta- Andria-Trani	388390	380	10058	0.77	66	295	17.4	2.2	2.9
Brindisi	390456	659	5795	0.85	67	100	10.2	2.0	1.7
Foggia	616310	1170	18639	1.02	161	655	13.8	2.6	3.5
Lecce	791122	521	6420	0.01	85	114	16.3	- <sup>†</sup>	1.8
Taranto	572772	281	10802	0.67	34	237	12.1	0.9	2.2
<b>Basilicata</b>	<b>556934</b>	<b>400</b>	<b>10055</b>	<b>0.72</b>	<b>36</b>	<b>214</b>	<b>9.0</b>	<b>0.9</b>	<b>2.1</b>
Potenza	360936	189	6739	0.83	27	156	14.3	0.9	2.3
Matera	195998	211	3316	0.50	9	58	4.3	0.9	1.7
<b>Calabria</b>	<b>1924701</b>	<b>1179</b>	<b>22191</b>	<b>0.51</b>	<b>129</b>	<b>368</b>	<b>10.9</b>	<b>1.3</b>	<b>1.7</b>
Catanzaro	354851	214	3134	0.40	31	49	14.5	2.2	1.6
Cosenza	700385	468	6676	0.78	48	176	10.3	0.9	2.6
Crotone	170718	119	2065	0.11	10	35	8.4	5.2	1.7
Reggio di Calabria	541278	294	8586	0.18	29	81	9.9	3.1	0.9
Vibo Valentia	157469	84	1730	1.12	11	27	13.1	0.6	1.6
<b>Sicily</b>	<b>4968410</b>	<b>3056</b>	<b>89352</b>	<b>0.37</b>	<b>342</b>	<b>2390</b>	<b>11.2</b>	<b>1.9</b>	<b>2.7</b>
Agrigento	429611	135	3651	0.19	24	107	17.8	3.0	2.9
Caltanissetta	260779	186	3733	0.00	18	81	9.7	- <sup>‡</sup>	2.2
Catania	1104974	779	26464	0.26	103	849	13.2	3.6	3.2
Enna	162368	438	2866	0.00	34	76	7.8	- <sup>‡</sup>	2.7

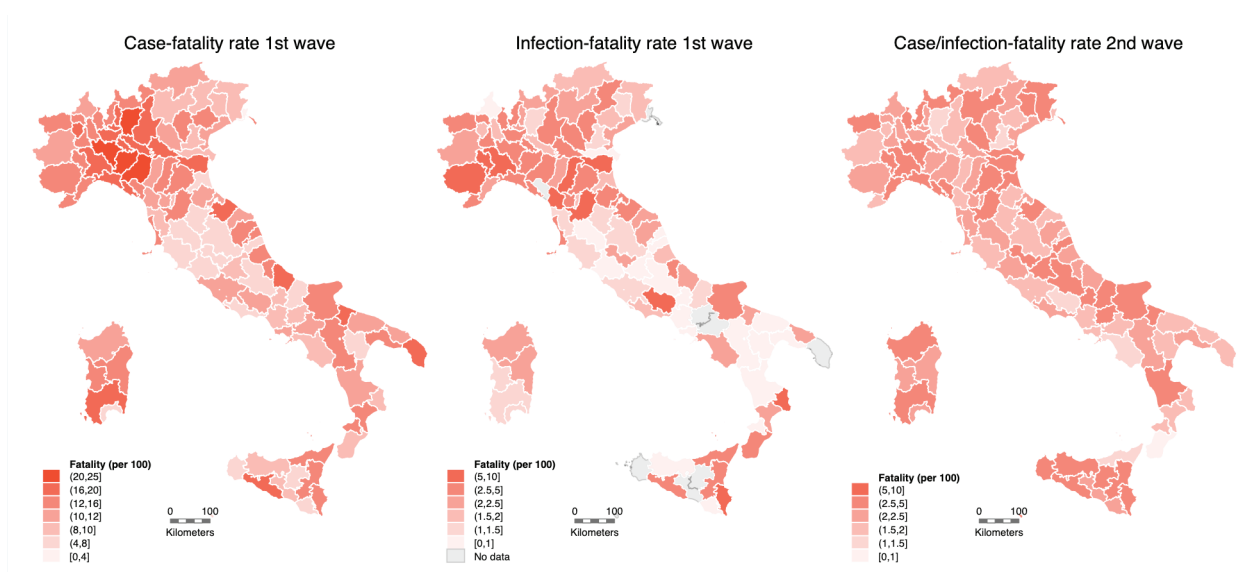
Region/ Province	Population Jan 1, 2020	Cases 1 <sup>st</sup> wave	Cases 2 <sup>nd</sup> wave	Seroprev. (%)	Deaths 1 <sup>st</sup> wave	Deaths 2 <sup>nd</sup> wave	Case- fatality rate 1 <sup>st</sup> wave	Infection- fatality rate 1 <sup>st</sup> wave	Case/ infection fatality rate 2 <sup>nd</sup> wave
Messina	620721	474	10246	0.32	59	136	12.4	2.9	1.3
Palermo	1243328	500	24929	0.89	43	665	8.6	0.4	2.7
Ragusa	321215	87	6490	0.30	6	161	6.9	0.6	2.5
Siracusa	397037	321	5112	0.14	47	162	14.6	8.8	3.2
Trapani	428377	136	5861	0.00	8	153	5.9	– <sup>‡</sup>	2.6
<b>Sardinia</b>	<b>1630474</b>	<b>1366</b>	<b>28920</b>	<b>0.50</b>	<b>145</b>	<b>712</b>	<b>10.6</b>	<b>1.8</b>	<b>2.5</b>
Cagliari	430914	253	6573	0.38	19	161	7.5	1.2	2.4
Nuoro	206843	78	6055	0.24	12	123	15.4	2.4	2.0
Oristano	156078	61	2416	0.43	8	51	13.1	1.2	2.1
Sassari	489634	875	8997	0.78	90	247	10.3	2.4	2.7
South Sardinia	347005	99	4879	0.42	16	130	16.2	1.1	2.7
<b>Italy</b>	<b>60244639</b>	<b>235839</b>	<b>1808260</b>	<b>2.49</b>	<b>35048</b>	<b>40392</b>	<b>14.9</b>	<b>2.2</b>	<b>2.2</b>

<sup>†</sup>Provinces excluded due to implausible data of seroprevalences since the estimated number of seroprevalent subjects are less than the number of positive cases at the end of the first wave. <sup>‡</sup>Provinces excluded due to missing/null data about seroprevalence.

(19.7%), and Piacenza (9.5%). Six provinces (Avellino, Benevento, Caltanissetta, Enna, Massa-Carrara and Trapani) reported null seroprevalence, while three provinces, Lecce, Gorizia and Trieste, showed extremely low and implausible seroprevalence rates. We considered these latter provinces as unwarranted outliers arising from a low and potentially highly biased participation in

the survey since the estimated number of seroprevalent subjects is lower than the ascertained cases during the first wave. For this reason, we removed these provinces from the analyses concerning the infection-fatality rate.

Figure 1 shows the case-fatality rate (from swab testing) and the infection-fatality rate (from seroprevalence data) in the first wave, and the case/



**Figure 1.** Crude case-fatality rate (deaths per 100 cases) for first wave (February 24–June 30, 2020), infection-fatality rate (deaths per 100 cases) after the first wave, and case/infection-fatality rate for the second (September 1–December 31, 2020) wave.

infection-fatality rate (from swab testing) in the second wave across the Italian provinces. Overall in Italy, crude case-fatality rate was 14.9% for the first wave and 2.2% for the second wave, while the crude infection-fatality rate based on seroprevalence after the first wave was 2.2%. Province-specific values of case-fatality rate showed a median value of 12% (ranging from 2.3% in Gorizia to 24.6% in Parma), while the infection-fatality rate using seroprevalence data was much lower with a median value of 2.2%. During the second wave, SARS-CoV-2 testing greatly increased and was extended also to asymptomatic subjects, leading to a 'mixed' case/infection-fatality rate with median value of 2.2%, comparable to the infection fatality rate of 2.2% (Table 1).

In Table 2 we report SARS-CoV-2 cases and COVID-19 deaths occurred in European countries in 2020 divided in the two pandemic waves, and the case-fatality and case/infection-fatality rates in European countries for the first and second waves, respectively. Overall, Italy showed one of the highest first-wave case-fatality rate (14.43%) along with other severely hit countries such as France (18.22%), Belgium (15.48), and UK (14.15%) compared to the value of EE/EEA area (10.59%) (Table 2 and Figure 2). In the majority of European countries, the second wave began from August to mid-September 2020, with some exceptions reporting an earlier onset in July, namely France, Spain, Malta, and Ukraine, with consequent difficulties in

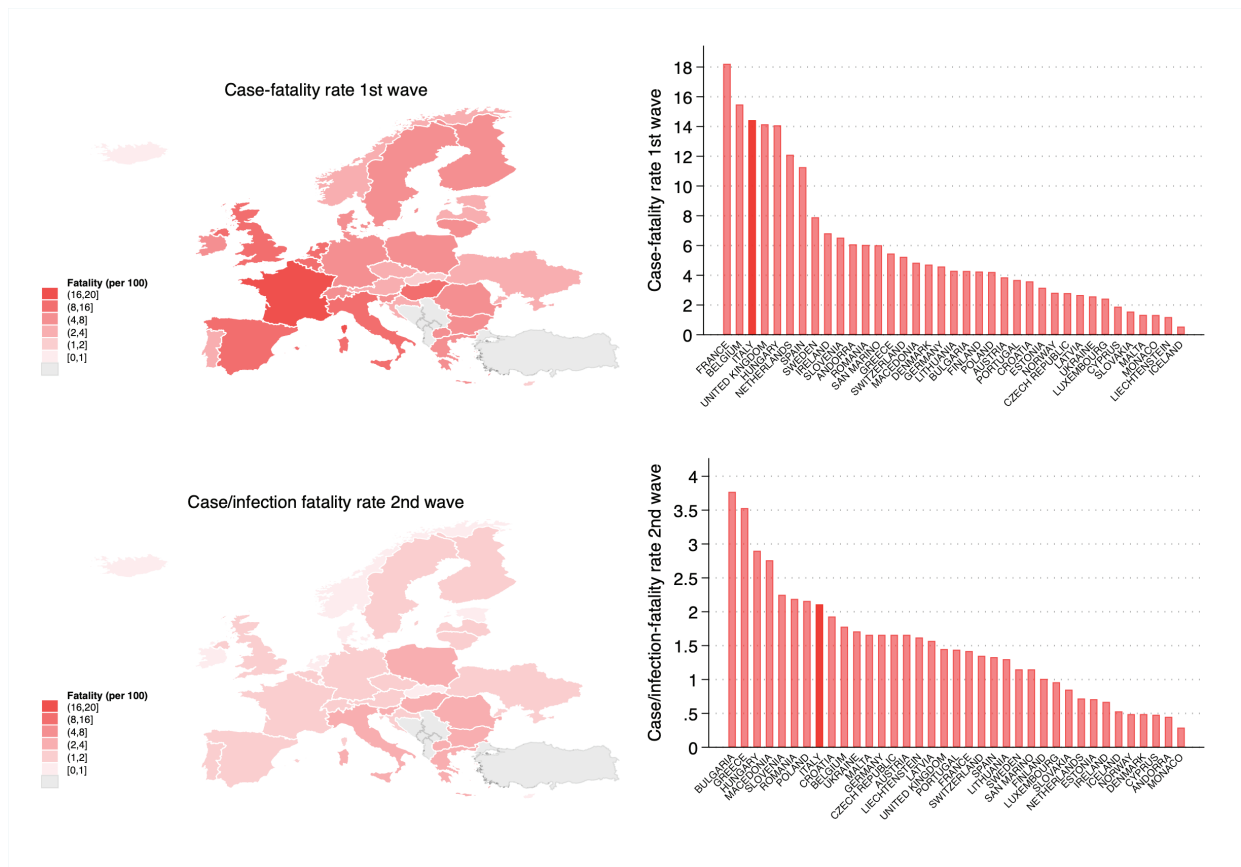
**Table 2.** Crude case-fatality (deaths per 100 cases) for the first (1st) wave for all EU/EEA countries (+ Switzerland and United Kingdom) from the beginning of the pandemic to June 30 if not differently specified, and case/infection-fatality rate (deaths per 100 cases) for the second (2nd) wave. Time-frame is different with the begin of the second wave indicated for each country, while the end was January 3, 2021 for all countries.

Country	Total population 2020 <sup>f</sup>	Cases 1 <sup>st</sup> wave	Deaths 1 <sup>st</sup> wave	Case-fatality 1 <sup>st</sup> wave	2 <sup>nd</sup> wave time-frame	Cases 2 <sup>nd</sup> wave	Deaths 2 <sup>nd</sup> wave	Case/infection fatality 2 <sup>nd</sup> wave	Total 2020 cases	Total 2020 deaths	2020 fatality
Andorra	76177	855	52	6.08	14 Sep	6848	31	0.45	8192	84	1.03
Austria	8901064	18269	706	3.86	14 Sep	331239	5497	1.66	364574	6253	1.72
Belgium	11522440	62394	9660	15.48	14 Sep	556759	9927	1.78	651968	19876	3.05
Bulgaria	6951482	5740	246	4.29	5 Oct	181464	6834	3.77	203051	7678	3.78
Croatia	4058165	3151	113	3.59	5 Oct	195299	3774	1.93	212958	4072	1.91
Cyprus	888005	1003	19	1.89	12 Oct	21988	106	0.48	23974	131	0.55
Czech Republic	10693939	12556	352	2.80	31 Aug	722615	12005	1.66	747003	12431	1.66
Denmark	5822763	12832	606	4.72	7 Sep	151164	747	0.49	168711	1374	0.81
Estonia	1328976	1993	63	3.16	23 Oct	25110	178	0.71	29521	251	0.85
Finland	5525292	7272	309	4.25	7 Sep	28628	289	1.01	36919	607	1.64
France	67320216	164068	29893	18.22	27 Jul	2457579	34845	1.42	2636772	65037	2.47
Germany	83166711	196554	9016	4.59	7 Sep	1524714	25249	1.66	1775513	34574	1.95
Greece	10718565	3519	192	5.46	10 Aug	134476	4745	3.53	140099	4957	3.54
Hungary	9769526	4183	589	14.08	31 Aug	322890	9363	2.90	328851	9977	3.03
Iceland	364134	1830	10	0.55	14 Sep	3589	19	0.53	5754	29	0.50
Ireland	4964440	25527	1741	6.82	7 Sep	72215	482	0.67	101887	2259	2.22
Italy	59641488	241611	34861	14.43	31 Aug	1887228	39855	2.11	2155446	75332	3.49
Latvia	1907675	1124	30	2.67	21 Sep	40972	644	1.57	42497	680	1.60
Liechtenstein	38747	84	1	1.19	5 Oct	2096	34	1.62	2222	35	1.58
Lithuania	2794090	1836	79	4.30	5 Oct	142802	1856	1.30	147987	1950	1.32
Luxembourg	626108	4522	110	2.43	14 Sep	39725	382	0.96	46919	506	1.08
Malta	514564	671	9	1.34	27 Jul	12520	208	1.66	13219	217	1.64
Monaco	39244	75	1	1.33	5 Oct	685	2	0.29	907	3	0.33
The Netherlands	17407585	50621	6127	12.10	31 Aug	750122	5383	0.72	820193	11598	1.41



Country	Total population 2020 <sup>†</sup>	Cases 1 <sup>st</sup> wave	Deaths 1 <sup>st</sup> wave	Case-fatality 1 <sup>st</sup> wave	2 <sup>nd</sup> wave time-frame	Cases 2 <sup>nd</sup> wave	Deaths 2 <sup>nd</sup> wave	Case/infection fatality 2 <sup>nd</sup> wave	Total 2020 cases	Total 2020 deaths	2020 fatality
Norway	5367580	8895	251	2.82	19 Oct	34579	171	0.49	50715	449	0.89
Poland	37958138	35950	1517	4.22	28 Sep	1235617	26729	2.16	1322947	29161	2.20
Portugal	10295909	43897	1614	3.68	7 Sep	371365	5356	1.44	431623	7196	1.67
Romania	19328838	28973	1750	6.04	21 Sep	527648	11544	2.19	640429	15979	2.50
San Marino	34453	698	42	6.02	12 Oct	1741	20	1.15	2493	62	2.49
Slovakia	5457873	1798	28	1.56	21 Sep	306848	2616	0.85	314117	2657	0.85
Slovenia	2095861	1700	111	6.53	7 Sep	122684	2761	2.25	125858	2891	2.30
Spain	47332614	251789	28388	11.27	6 Jul	1702891	22672	1.33	1958844	51078	2.61
Sweden	10327589	70612	5576	7.90	5 Oct	366858	4232	1.15	462661	10125	2.19
Switzerland	8606033	32184	1685	5.24	5 Oct	405397	5455	1.35	459660	7238	1.57
Ukraine	43733759	48500	1249	2.58	20 Jul	1015251	17369	1.71	1074093	18854	1.76
United Kingdom	68059863	287121	40632	14.15	7 Sep	2307627	33473	1.45	2654779	75024	2.83
<b>EU/EEA countries</b>	<b>45309377</b>	<b>1264974</b>	<b>133967</b>	<b>10.59</b>	-	-	-	-	<b>15963232</b>	<b>379360</b>	<b>2.38</b>

<sup>†</sup>Population data from Eurostat (47).



**Figure 2.** Map and histograms of case-fatality and case/infection-fatality during the first and second waves in EU/EEA countries (+ Switzerland and United Kingdom).

**Table 3.** Number of influenza cases and deaths in Italy during the most recent seasonal flu epidemics.

Season	Flu cases	ISTAT report	Flu deaths
2012/2013	5995000	2013	417
2013/2014	4542000	2014	272
2014/2015	6299000	2015	675
2015/2016	4876900	2016	316
2016/2017	5440900	2017	663
2017/2018	8677300	2018	745

the comparison. Overall in 2020, the EE/EEA area showed a fatality rate of 2.38%, with the highest values reported by Bulgaria (3.78%), Greece (3.54%), and Italy (3.49%).

In Table 3, we report data about cases of seasonal flu epidemics, and we computed an average case-fatality rate from past seasons of 0.01%, which is orders of magnitude lower of COVID-19 disease.

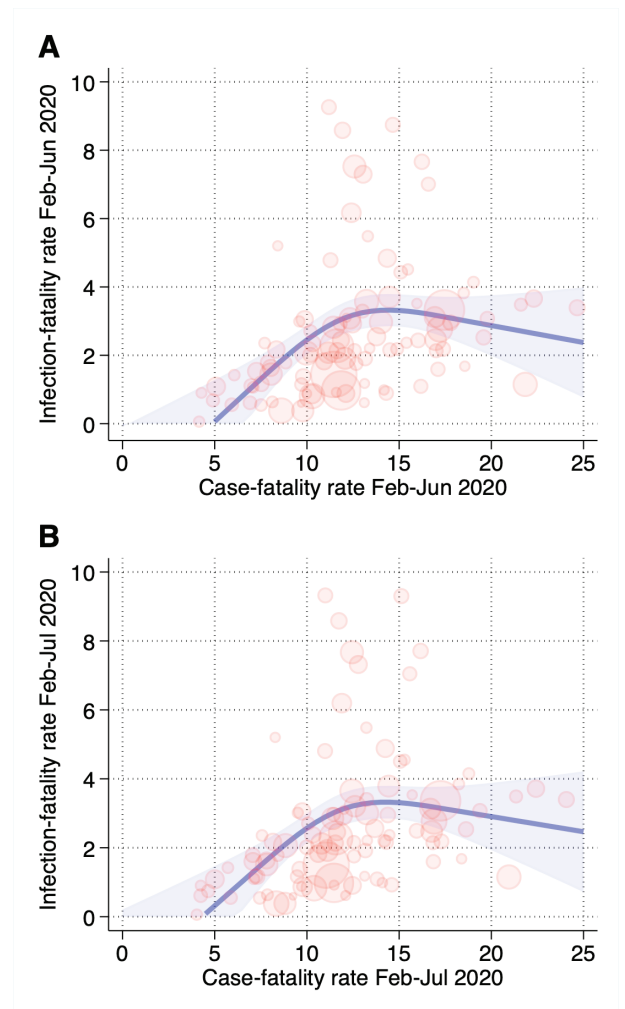
When we compared the case-fatality rate of the first wave with the infection-fatality rate after the first wave using seroprevalence data in the Italian provinces using the spline analysis (Figure 3), we found a substantially linear positive association up to approximately 12% of case-fatality rate in the first wave corresponding to 3.6 infection-fatality rate, while the curve flattened at higher values.

In the spline regression model comparing case-fatality rate in the first wave with the case/infection-fatality rate in the second wave, we did not find any relation between the two variables. On average, the case-fatality rate was 5.6 times 95% CIs (95% CI 5.2-6.1) higher in the first compared to the second wave (Figure 4).

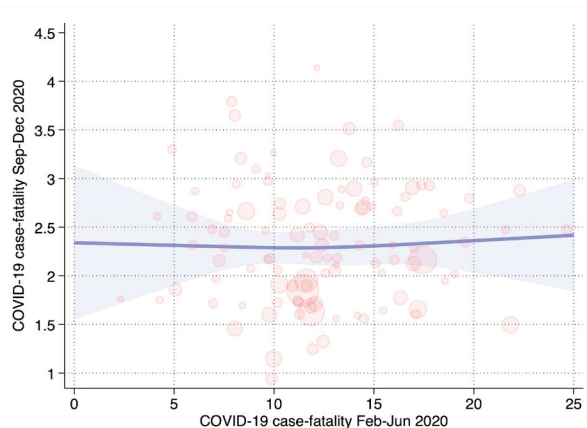
## Discussion

At the end 2020, Italy was one of the countries reporting the highest number of confirmed positive cases as well as COVID-19 deaths (52). Since many uncertainties still exist about the real impact and severity of COVID-19 pandemic (33,37,53,54), in the present investigation we provided an assessment of the COVID-19 case-fatality and infection-fatality rates during the 2020 in Italian provinces.

Overall, our data confirmed that during the first wave, when almost all subjects underwent SARS-CoV-2 testing due to presence of symptoms related to COVID-19, the Italian case-fatality rate was as high as around 15%, being much higher than the infection-fatality rate. Conversely, during the second wave, the case/infection fatality rate we could compute waned to a much lower value of 2.2%. The most plausible explanation for this discrepancy is the hybrid nature of the latter



**Figure 3.** Comparison of first wave case-fatality rate (using positive swab data to estimate COVID-19 cases) and infection-fatality rate (using May-June seroprevalence data to estimate infected cases) considering the time frames February 24-June 30, 2020 (A) and February 24-July 31, 2020 (B). Spline regression model adjusted for aging index, percentage commuting outside the municipality of residence on a daily basis, and percentage of dwellings occupied by only one resident.



**Figure 4.** Comparison of first and second wave case-fatality rate in a spline regression model adjusted for aging index, percentage commuting outside the municipality of residence on a daily basis, and percentage of dwellings occupied by only one resident.

estimate, due to the different policy for SARS-CoV-2 infection assessment. In fact, during the first wave only suspected cases due to travelling from high risk countries or with symptoms suggesting of COVID-19 were tested (55), while during the second waves also asymptomatic cases underwent swab testing. These findings appear to be confirmed by the assessment of the infection-fatality rate estimated through seroprevalence data, almost identical to COVID-19 fatality during the second wave, with the same overall national value of 2.2%. In addition, the comparison of the COVID-19 fatality rates in other European countries demonstrated generally a higher case-fatality rate for Italy during the first wave, and a marked decrease during the second wave that could have been at least partially due to the increase of population screening with SARS-CoV-2 swab testing of a large proportion of asymptomatic individuals (55). However, since the availability of SARS-CoV-2 molecular testing increased all over Europe during the second wave, our results may also indicate that the severity of the disease and the spread of the infection decreased in Italy with time during 2020, as compared with the other European countries, for reasons possibly related to the higher severity of the first wave, such as a larger prevalence of immunity in the population, or the increased depletion of highly susceptible individuals due to the high first wave COVID-19 mortality (56-59).

Interestingly, our results are partially conflicting with data from a recent meta-analysis suggesting much lower value (2.7%) during the first wave in European region (33) but higher estimates for Italy with a mean value of 7.8% (median=8.58%) and range from 1.7% up to 14.5%. This high heterogeneity could be explained by the modality of case-fatality assessment among different studies. In particular, the lower value was reported from a study implementing modelling techniques, e.g. SEIR (Susceptible-Exposed-Infective-Recovered) model (60), as well as when based on incomplete data when the first wave was still ongoing (61). Conversely, studies using real and comprehensive data demonstrated similar or even higher estimates compared with the present study (62-64). Interestingly, a comparable pattern of discrepancies in the estimation of case-fatality rate can be noted also for other countries severely hit by the pandemic such as United Kingdom and France (33). For these reasons, despite such modelling demonstrated a high reliability in the prediction of pandemic tend/curves (65,66), the estimation of disease case-fatality was not so effective and reliable, also since that the number of infections and deaths may be affected by other determinants, in particular the advances in SARS-CoV-2 infection as well as COVID-19 diagnosis (67), and especially treatment (68-70).

The occurrence of a high case-fatality rate in Italy was not entirely unexpected, being explained by the demographic and health characteristics of the Italian population. Also, at the very beginning of the pandemic in Italy, a case-fatality rate of 7.2% was estimated by the National Institute of Health (71), much higher compared with the one reported in China (72). Indeed, COVID-19 demonstrated to be more severe and deadly in vulnerable individuals due to older age and/or comorbidities (73,74), leading to a higher mortality in older subjects (75). Similarly, our findings are consistent with the recent report of the National Institute of Statistics, as they found a slightly higher (sex and age-adjusted) case-fatality rate of 4.3% in the entire 2020 (52). Consistently with our findings, such analysis yielded a higher value in the first pandemic period (although based on a slightly different time-frame, February-May 2020), i.e. 6.6%, a lower value

in June–September (1.5%), and again a slightly higher value in October (2.4%).

Results of the seroprevalence nationwide survey confirmed that some Northern Italy areas were heavily affected during the first wave (76), especially the provinces of Bergamo, Brescia, Lodi, Cremona in Lombardy region, and Piacenza and Parma in Emilia-Romagna region (14). Such provinces were those that experienced the highest decrease in the hybrid case/infection fatality rate we could compute for the second wave, consistently with a pattern we have documented for COVID-19 incidence (14).

Our results indicated that the case–fatality rate of COVID-19 was much higher as compared with influenza through 2020 and independently from the time period, indicating that COVID-19 should not be considered a simply flu-like syndrome (77,78), with much larger implications in terms of population and public health burden. This further confirms how relevant is the implementation of effective preventive medicine measures against SARS-CoV-2 infection and COVID-19 including but not limited to vaccination, also in the absence of most effective therapy for this disease (79). Finally, our findings are particularly relevant from a public health perspective since they highlight how different was the impact of the COVID-19 pandemic compared to the seasonal flu and other outbreaks, taking into account the number of affected people and deaths, the health care systems overload, and the psychological and economic burden (80–82).

Our study has some limitations. First, we used aggregated data at a provincial level, showing much higher level of geographical detail than the previous ‘regional’ analyses but still not entirely homogeneous in terms of population size characteristics, despite we tried to control for some potential confounders. In addition, we could not calculate sex- and age-standardized estimates, and therefore the comparison across different geographical areas must be made with caution (83).

Strengths of our analysis include the assessment of the COVID-19 severity during the first two pandemic waves when there was no circulation of virus variants (43), making unlikely this possible confounding related to differences in virus transmission and severity (84,85). Similarly, the vaccination campaign effectively began in January 2021 (86), thus not

affecting the susceptibility of subjects and the reliability of our analysis.

## Conclusions

Our findings demonstrate that COVID-19 severity in Italy, as assessed through either case–fatality or infection–fatality rates, has been much higher compared with other airborne infections like influenza, while being substantially similar to a few other Western European countries. They also indicate that COVID-19 case–fatality rate and infection fatality rate substantially differ, though such measures are difficult to assess, due to methodological issues and potential biases that can affect these estimates. An adequate assessment of COVID-19 severity may also be of major relevance to plan and test public health interventions aimed at curbing the spread of SARS-CoV-2 infection.

**Conflict of interest:** Each author declares that he/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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