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The COVID-19 History in Italy: Correlations with Environment, Demographic Variables and Chronic Diseases Therapy

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ABSTRACT

Background: *COVID-19 still represents a very serious problem in Italy.*

Objective: *To correlate the COVID-19 deaths in Italy with clinical, therapeutic, demographic and social variables.*

Material and Methods: *The data of positive cases and deaths due to COVID-19 from 1st March to 4th May in Italy were taken from the official documents and collected for clinical, therapeutics, demographic and social variables. The correlations were calculated in linear terms.*

Results: *The COVID-19 outbreak had affected the most productive areas. In a period of less than 2 months 211,938 subjects were found positive and 29,079 people died (13.7 %). The peak of the curves was reached within 3-4 weeks and the decline over time seems to be asymptotic. The entire life cycle of the virus is expected to minimize in about six months provided that adequate measures will be maintained.*

Positive correlations were found with pneumonia, cancer and infective diseases, while no correlation was shown for heart ischemic and musculoskeletal diseases or viral hepatitis. In relation to drugs, significant negative correlations were evident with those used in many chronic diseases and flu vaccination.

Significant positive correlations were shown with population density, GDP, river kilometers and domestic water consumption.

Conclusions: *COVID-19 is behaving like an independent disease, particularly affecting the most prosperous regions and causing a higher number of deaths, 80 times more than that of the seasonal flu. Therapies for some chronic diseases and the seasonal flu vaccines have been shown to have a positive impact. The influence of water in terms of viral spread is still an overt problem to be solved.*

Keywords

Coronavirus, Clinical condition, Cardiovascular diseases, Demographic variables, Social variables, Water pollution, Vaccines.

Introduction

It has already been reported [1] that Italy may represent a model for the COVID-19 epidemic since in some of the Italian regions, the disease was extremely aggressive, while in some of the other parts, especially in Southern Italy and the islands, it was far less widespread.

The positive cases and deaths in the world up to 4th May accounted for 3,584,322 confirmed cases causing 251,580 deaths (7.2 %). In Italy 211,938 positive cases and 29,079 deaths were reported in the same period with a higher ratio (13.7 %) [2] And most of the deaths were recorded as interstitial pneumonia.

In relation to the positive cases, the figures belong to the swabs taken and because of the different policy among the countries it is hard to make any correct comparison. The same goes for deaths, given that no common worldwide criteria have been firmly established. Furthermore, in some countries elderly people who died in the nursing homes or at home were not considered within the figures.

Italy was one of the most affected countries in the world. One aspect seems to be clear from the analysis of the curves in Italy, the trends (positive cases and deaths) appear as asymptotic, and one may expect a very long period of time to eradicate this virus. Furthermore, a possible second wave can be expected after the end of the lockdown when people get back to their usual activities and also because most of the cases are asymptomatic.

The correlations between the viral diffusion and the demographic, social, and ecological variables indicate that the population density, the number of companies in the territories, the GDP, the flat land, the mountains (not the hills), the linear km of rivers, the domestic water consumption are positively correlated with the viral spread, while no correlation is shown with the temperature and the rainfall characteristics of the territories [1].

With regard to age and diseases, despite some statements [3], the available data up to 19th May do not provide an evident correlation with the aging indexes, diabetes, obesity, cardiovascular diseases (CVDs) and smoking [4].

In conclusion, it seems that COVID-19 pneumonia is behaving like an independent disease.

The aggressiveness of the viral spread could be the basis for the inclusion of COVID-19 in the human meta- organism as for other RNA viruses (such as AIDS and hepatitis) with the characteristics of a specific target organ: the lungs.

After the explosion of the disease, while waiting for a suitable vaccine to become available, a tentative plan to find a therapy (prophylactic and/or also preventive) started worldwide.

Many potential therapeutic tools were suggested [5], such as the inhibitors of antiretroviral (protease already in use for HIV infection) or antivirals. However, the clinical results of the combination lopinavir/ritonavir were disappointing [6].

Remdesivir, originally developed for Ebola, was shown to accelerate the recovery from COVID-19 following IV infusion for 10 days [7]. The authors' conclusion was that"*Remdesivir was adequately tolerated but did not provide significant or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reduction in some clinical parameters*".

Hydroxychloroquine (HCQ) was also studied [8]. The conclusion of the authors was "*The administration of HCQ did not result in a higher negative conversion rate but improvement and alleviation of clinical symptoms than the standard of care (SOC) alone.... possibly through anti-inflammatory effects. Adverse events were significantly increased in HCQ recipients but no apparent increase of serious adverse events*".

Favipiravir was also tested in comparison to an antimalarial Arbidol [9]. The conclusions of the authors were *"favipiravir can be considered as a preferred treatment because of its higher 7-day clinical recovery rate and more effectively reduced the incidence of fever, cough except some antiviral-associated adverse effect*".

The activity of plitidepsin, a depsipeptide [10] which has been approved by EMA (European Medicine Agency) as an orphan drug for treatment of lymphoblastic leukemia in Europe, is under study in Spain and the results are not yet available.

Monoclonal antibodies (47D11) against the trimeric spike glycoprotein (S) were isolated and humanized, chimeric IgG1 antibodies seem to inhibit the *in vitro* infection of COVID-19 in Vero E6 cells [11].

In the end, many different approaches have been used and each compound that has a direct or indirect antiviral activity can be a candidate (see discussion).

Since pneumonia caused by COVID-19 is also characterized by the formation of thrombotic events, it was considered important to follow treatment with LMWH (Low Molecular Wight Heparin) or with other antithrombotic agents as a prophylaxis [12].

COVID-19 is frequently concomitant with other diseases. In a sample of 25,452 cases in Italy [3,13], the most common diseases were hypertension (69.2% of the cases) followed by ischemic heart disease (28.2 %) and chronic kidney failure (21.0 %). More than half of the cases (60.3 %) were affected by 3 or more chronic diseases. However, an analysis that includes more variables is needed.

The aims of the present study were: a) to analyze the correlations between the deaths of COVID-19 and the most common diseases; b) to analyze the impact of concomitant chronic therapy on the death rate; c) to analyze the importance of some environmental and demographic variables.

Material and Methods

The time period considered was from 1st March to 4th May when lockdown restrictions were already in place over the past 2 months (65 days).

The data on COVID-19 positive cases and deaths – confirmed or presumed viral infections- were taken from the daily Official Bulletin and publicly released by the Department of the Italian Protezione Civile [3,13].

The demographic variables, population, density/km^2, life expectancy [14] and the Gross Domestic Product (GDP) [15] were considered.

The number of cardiovascular diseases were retrieved from specific mortality indexes [16]; old age indexes were taken for the year 2019 [17]; data concerning the water consumption were also considered; the length, the route, and territories of the main Italian rivers were taken [19]; mobile data traffic was also considered [20].

The number of vehicles (cars and buses) was retrieved from official records [21] as was the data on smoking [22]. The data relative to deaths were taken from 2018 [23] being the only data available. Data concerning the defined daily dose of drugs (DDD/1000 inhabitants) were considered [24]. The differential values of people affected by the viral infection (D) were calculated consistent with the values taken on the day N_n - $N_{n-1.}$ As a simple index of the viral spreading.

Statistical methods

The averages and SD were calculated for all variables. For the correlations, "r" values were calculated using $p < 0.05$ as cut-off for the statistical significance. This simple method was found to be more severe than the relative corrections through Robust Regression (which were not reported).

Results

The trends of COVID-19 positive cases and deaths

The trend of the COVID-19 positive cases is reported in Figure 1. Data recorded every three days were taken.

The number of deaths in the same period is reported with the same interval of time (3 days) as represented in Figure 2.

The % of deaths/ positive cases of COVID-19 is presented in Figure 3.

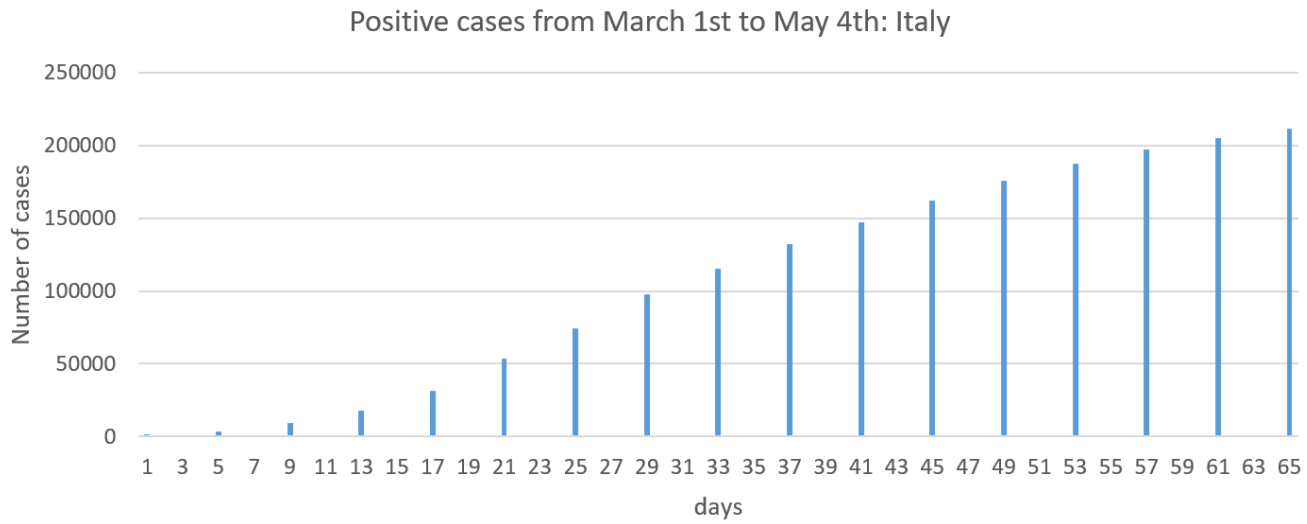

Figure 1: Positive cases of COVID-19 in Italy from 1st March to 4th May 2020: data every three days.

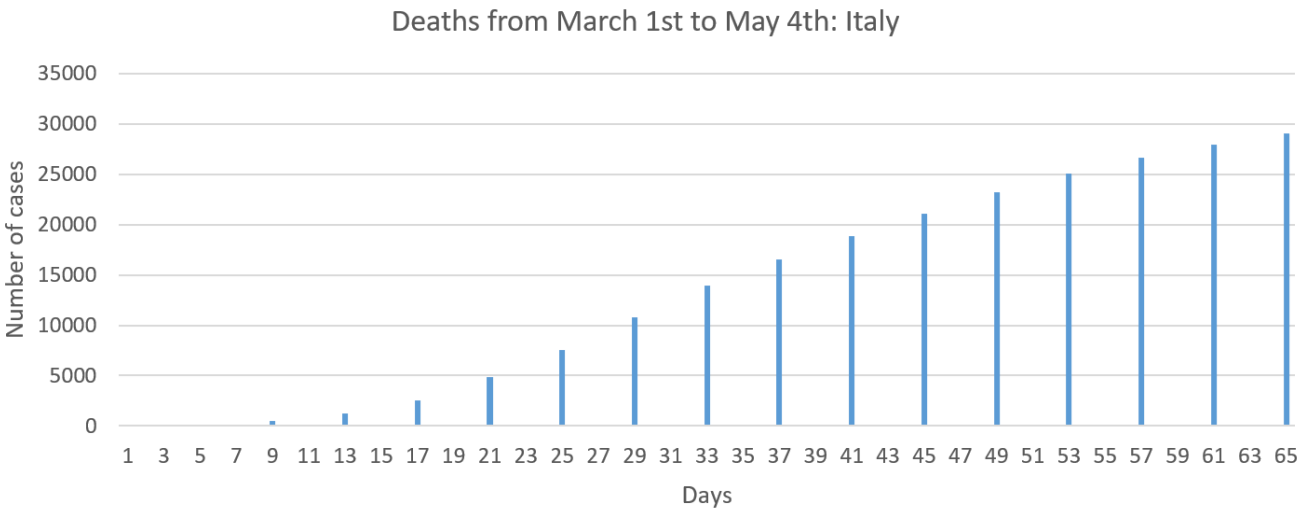

Figure 2: Deaths from COVID-19 in Italy from 1st March to 4th May 2020: data every three days.

The ratio grew up to the value of 13.7 %. This value depends upon the number of oropharyngeal swabs (OPS) and was stabilized when the OPS were done approximately in the same daily amount. Deaths and positive cases have a very high significant correlation ($r= 0.9863$; $p<0.0001$).

The differentials (D) are reported in Figures 4 and 5. In this case, the daily data were considered to provide a clearer picture of the descending trends of both positive cases and deaths.

The decay of the positive cases and deaths is according to "waves" with a period of about 4 days. The Rodbard 4PL Logistics equation feathering [25] shows asymptotic values with a stable condition approximately around June 15th, provided that the spread will not resume after the lockdown restrictions.

Number of positive cases, deaths, OPS (oropharyngeal swabs)

Deaths due to COVID-19 and expected deaths due to pneumonia in 2020 in the different Italian regions are reported in Table 1.

In some of the regions, deaths attributed to COVID-19 were more than one order of magnitude (in a range between 2.1 and 33.8) compared to expected pneumonia deaths in the same period. These cases created an unpredictable crisis in the ICUs, especially in Northern Italy.

Causes of death from different diseases and correlation with COVID-19 positive cases and deaths

The causes of death from the most common diseases are reported, considering only the publicly available data (year 2017). Since the data of the year are highly correlated over time ($r > 0.85$) the comparison can be considered reliable. Life index was also considered and data are shown in Table 2.

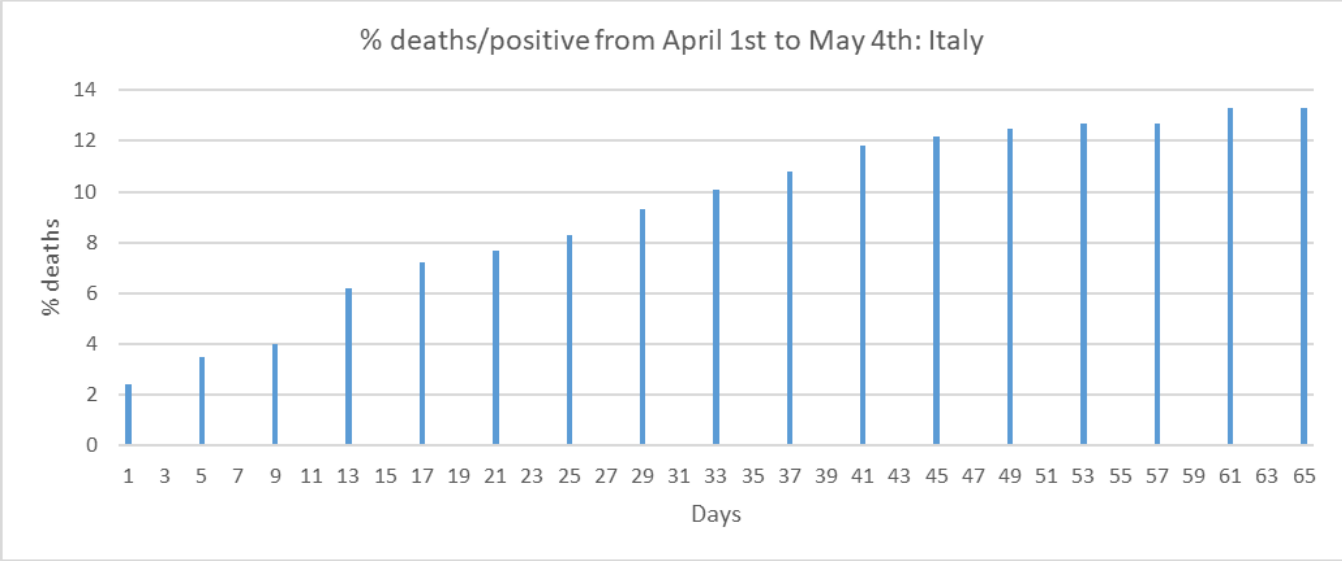

Figure 3: Percentage of deaths vs positive cases of COVID-19: from 1st March to 4th May.

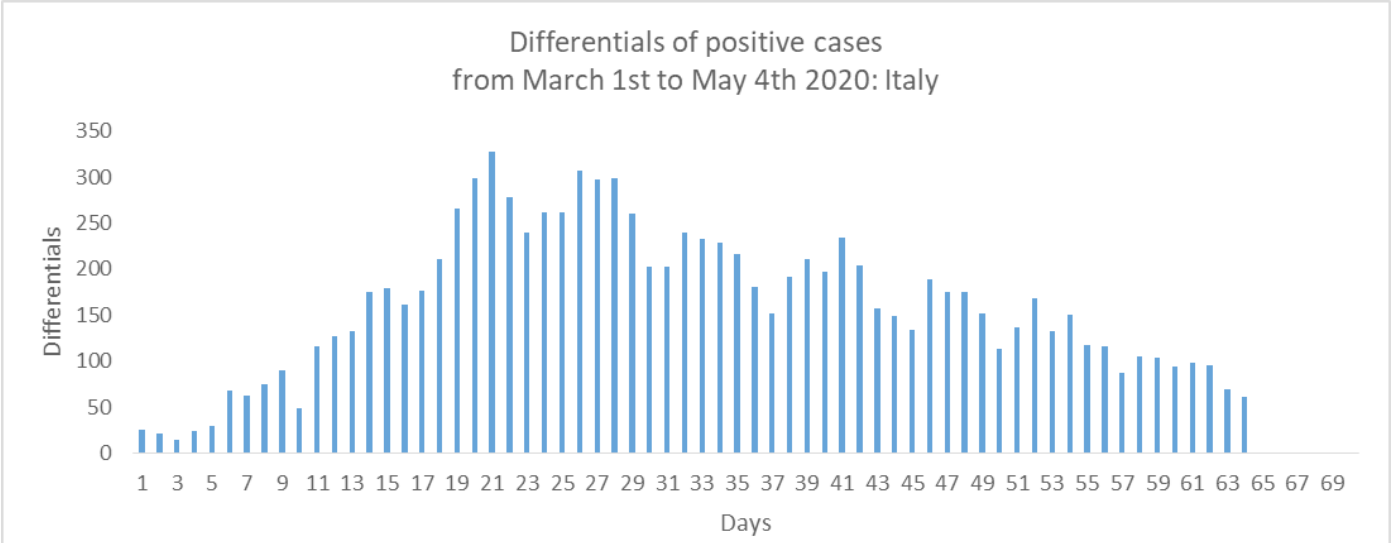

Figure 4: Differential values (day N_n - N_{n-1}) of the positive cases: daily data from 1st March to 4th May 2020.

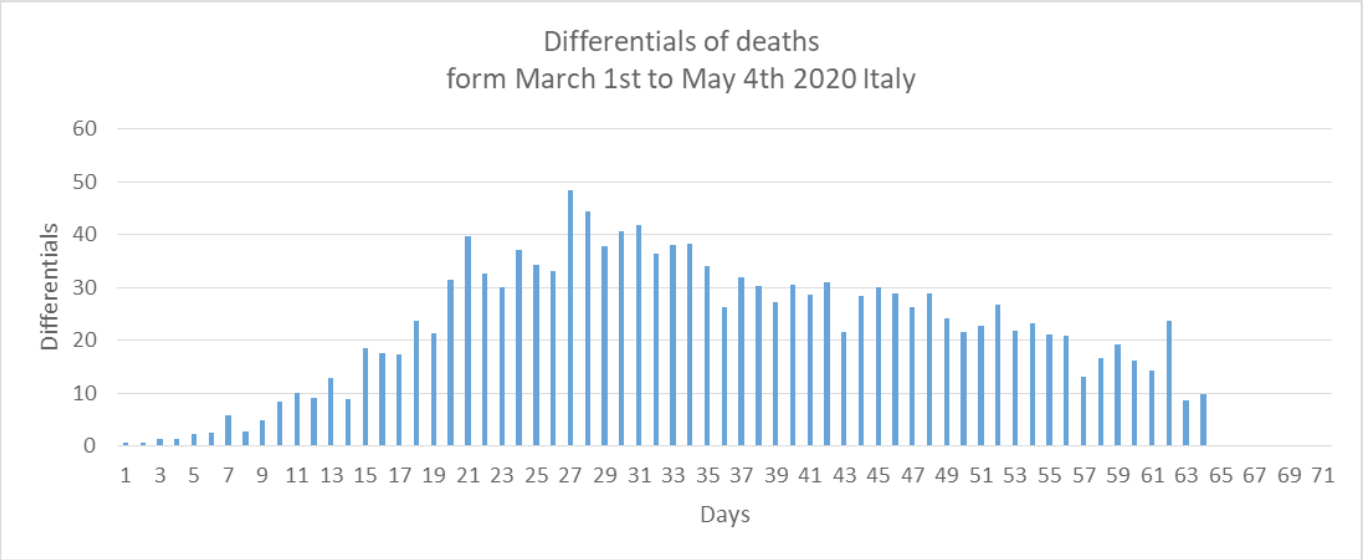

Figure 5: Differential values (day N_n - N_{n-1}) from COVID-19 deaths; daily data from 1st March to 4th May 2020.

Region	Inhab N x 10^3	OPS total	OPS/ Inhab N x 10^3	OPS Positive N	Deaths COVID-19 N	Pneu Exp[a] N	COVID-19/ Pneu Exp	Part of Italy
Lombardia	10.02	17333	1.73	78105	14294	423	33.8	North
Lazio	5.90	23067	0.39	6847	524	250	2.1	Center
Campania	5.84	36153	0.62	4498	366	73	5.0	South
Sicilia	5.06	51373	1.02	3255	244	109	2.2	Island
Veneto	4.91	163757	3.34	18373	1528	221	6.9	North
Emilia Romagna	4.45	90894	2.04	26175	3666	243	15.1	North
Piemonte	4.39	73192	1.67	27622	3186	239	13.4	North
Puglia	4.06	43119	1.06	4153	429	77	5.6	South
Toscana	3.74	85946	2.30	9601	881	182	4.8	Center
Calabria	1.97	22847	1.16	1118	88	23	3.9	South
Sardegna	1.65	14160	0.86	1317	119	42	2.8	Island
Liguria	1.57	21979	1.40	8412	1221	85	14.4	North
Marche	1.53	28006	1.82	6363	932	77	12.1	Center
Abruzzo	1.32	22552	1.71	3000	332	40	8.3	Center
Friuli Venezia Giulia	1.22	28777	2.36	3076	299	74	4.1	North
Trentino Alto Adige	1.06	32436	3.05	6799	714	30	23.9	North
Umbria	0.89	17099	1.92	2394	70	40	1.8	Center
Basilicata	0.57	6868	1.20	386	25	12	2.1	South
Molise	0.31	3683	1.19	301	22	9	2.6	South
Val d'Aosta	0.12	3910	3.08	1143	139	6	22.5	North
Total	60.59	943151		211938	29079	2253	range	
% Inhab		1.56					2.1-33.8	
r OPS Vs COVID-19 positive	***0.8112***							
r OPS Vs COVID-19 deaths	***0.7538*** .							

Table 1: COVID-19 positive cases and deaths, number of OPS/Region and expected deaths for pneumonia: data from 1st March to 4th May in the different Italian regions.

Statistically significant correlations ($p<0.05$) are reported in bold italic characters.

Legenda: a = expected pneumonia deaths in 2 months; OPS= oropharyngeal swabs; Inhab = inhabitants.

Deaths from COVID-19 are significantly correlated with cancers, pneumonia and infectious diseases. No significant correlations were found with life index, viral hepatitis, heart ischemic diseases, Alzheimer's disease and SCA (muscle skeletal apparatus). Diabetes and smoking also were not correlated (data not reported).

Deaths from pneumonia showed a different pattern of correlations (positive for cancers, respiratory and infectious diseases and also for SCA), meaning that COVID-19 behaves as a specific type of pneumonia.

Correlations of COVID-19 deaths with the common therapies

Most of the common drugs used in terms of defined daily dose (DDD according to WHO) were correlated with the COVID-19 deaths to determine if some of the commonly used drugs could interfere with the COVID-19 death rate. Data are reported in Table 3 and 4.

All the categories are negatively correlated with COVID-19, a part from N, L, S, P. Patterns of COVID-19 and pneumonia are different since the use of heparins/anti-aggregating products and drugs for pneumonia and for the cardiovascular system were not significantly correlated (class B and C). The pattern of COVID-19 deaths on the whole is different from pneumonia, with positive correlations with S and P. The two diseases showed the same negative correlation for J, D, A, G, and M.

Correlations of COVID-19 deaths with ecological, demographical, social variables

Some of the most common variables to describe the population were analyzed in the different Italian Regions to focus on the possible correlations with COVID-19 deaths: pneumonia was also considered. The data are reported in Tables 5 and 6. The patterns of COVID-19 and pneumonia are very different.

The COVID-19 death was significantly positive for all the variables apart from the inhabitants in hill residences and cell phone use. The only negative correlation was shown with the number of buses/1000 inhabitants. Pneumonia was positively correlated only with the population density, GDP and internet connections, while a negative correlation was shown with the number of buses/1000 inhabitants.

Region	Life index	All cancers	Isch heart disease	Respir disease	Pneum	Alzheimer's disease	Infectious disease	SCA disease	Viral hepatitis
Lombardia	165.5	31691	9654	8264	2537	2450	1741	552	410
Lazio	162.6	17539	7181	5274	1500	1131	998	156	168
Campania	129.8	14835	6977	4076	435	870	447	219	265
Sicilia	153.7	13230	5217	4149	653	970	409	255	221
Veneto	172.1	14284	5092	3925	1324	854	973	281	134
Emilia Romagna	182.6	14394	5098	4561	1457	587	1394	309	185
Piemonte	205.9	14769	4736	4687	1431	865	1005	373	161
Puglia	168.6	10516	4284	3331	462	936	532	215	231
Toscana	204.6	12180	3986	3820	1094	1142	906	308	155
Calabria	163.3	4520	2222	2495	137	285	245	98	92
Sardegna	212.0	5006	1417	1228	253	486	266	115	104
Liguria	255.8	6057	2162	1896	509	404	487	141	72
Marche	196.2	4720	2211	1512	463	558	434	90	47
Abruzzo	191.8	3677	2087	1189	239	417	228	109	45
Friuli Venezia Giulia	217.2	4260	1645	1366	442	179	287	71	40
Trentino Alto Adige	138.5	2719	1160	668	179	183	154	61	15
Umbria	204.2	2887	1371	953	240	244	231	73	28
Basilicata	193.2	1512	719	576	73	116	95	25	37
Molise	217.5	892	538	272	51	69	33	25	6
Val d'Aosta	181.6	397	131	140	37	22	23	9	4
M SD	185.84 30.126								
Total		170636	67699	53372	13516	12768	10848	3485	2420
r Vs COVID-19 Deaths	-0.1266	***0.4583***	-0.2539	0.2685	***0.5380***	-0.0094	***0.4419***	0.2579	-0.2267
r Vs Pneumonia Deaths	-0.1477	***0.8852***	0.1003	***0.7487***	1	0.1284	***0.8666***	***0.4500***	-0.3591

Table 2: Number and cause of death from the main diseases in the Italian regions (year 2017): correlations of the different variables with COVID-19 and pneumonia.

Statistically significant correlations ($p<0.05$) are reported in bold italic characters.

Legenda: Life index = % > 65 years Vs <14 years: Isch heart disease = ischemic heart disease; Resp disease = Respiratory diseases; Pneum = pneumonia; SCA= muscle skeletal apparatus.

Region	C	A	B	N	R	G	M
Lombardia	450.1	147.2	75.9	65.8	37.0	37.0	27.2
Lazio	482.1	162.0	108.0	60.8	38.0	42.9	44.6
Campania	505.6	185.5	77.7	54.8	57.7	42.4	44.4
Sicilia	497.7	180.1	83.7	43.7	43.2	40.5	43.7
Veneto	460.5	130.1	61.5	57.8	33.1	35.0	27.9
Emilia Romagna	460.3	117.3	90.7	60.2	34.3	37.2	29.0
Piemonte	436.8	135.4	83.7	68.5	34.2	38.8	32.2
Puglia	492.2	176.7	109.7	58.6	50.6	42.8	58.9
Toscana	449.2	131.3	92.8	78.1	40.1	38.4	33.8
Calabria	448.4	177.4	100.9	62.8	42.1	41.3	52.2
Sardegna	454.7	166.2	87.4	71.3	46.5	40.1	49.1
Liguria	405.2	144.3	60.6	72.1	39.7	40.2	28.7
Marche	479.6	145.6	90.4	67.0	36.2	47.4	43.2
Abruzzo	452.6	159.9	110.2	72.1	37.7	40.3	47.5
Friuli Venezia Giulia	474.0	137.6	96.1	56.4	34.2	34.4	34.3
Trentino Alto Adige	377.0	116.0	81.0	65.6	33.8	33.4	27.3
Umbria	555.6	147.6	86.3	72.7	37.1	43.3	35.4
Basilicata	453.3	164.0	96.0	56.3	44.7	43.8	46.6
Molise	445.2	144.8	102.4	59.9	33.9	37.0	42.7
Val d'Aosta	379.0	128.0	67.7	58.2	37.4	37.9	34.0
M	458.0	149.9	88.1	63.1	39.6	39.3	39.1
SD	41.25	20.83	14.72	8.07	6.38	9.30	9.33
r Vs COVID-19 deaths	***-0.5481***	***-0.5902***	***-0.5481***	0.1902	-0.4283	***-0.4828***	***-0.6737***
r Vs Pneumonia deaths	-0.1549	***-0.7412***	-0.3189	0.3385	***-0.6829***	***-0.4466***	***-0.7032***

Table 3: DDD (defined daily dose) of some drugs: correlations with COVID-19 and common pneumonia deaths.

Statistically significant correlations ($p<0.05$) are reported in bold Italic characters.

Legenda: C= cardiovascular system (mainly statins and antihypertensives); A = Gastrointestinal and metabolism (mainly pump inhibitors, vitamin D and insulin); B= Blood (mainly heparins and anti-aggregating agents); N= Central nervous system (mainly antidepressant, antiepileptics); R= Respiratory system (mainly anti asthma, anticholinergics, glucocorticoids); G= Genitourinary (mainly antiprostatic and estrogens); M= Musculoskeletal system (mainly bisphosphonates, NSAIDs);

Region	H	**J**	S	Vaccine[A]	L	D	P
Lombardia	25.2	17.7	16.7	12.9	8.4	2.8	1.1
Lazio	42.4	23.2	22.0	15.5	6.1	4.4	0.9
Campania	32.1	29.4	17.3	15.9	5.5	6.8	0.7
Sicilia	33.8	24.7	16.5	16.0	5.7	5.3	0.7
Veneto	28.8	15.0	18.1	16.0	6.4	3.3	1.0
Emilia Romagna	38.2	16.6	23.3	17.5	2.6	3.3	0.9
Piemonte	32.8	16.3	22.3	15.3	6.0	3.2	0.8
Puglia	42.3	27.2	18.6	17.0	6.0	4.4	0.5
Toscana	39.6	19.1	25.6	19.1	1.4	4.1	1.1
Calabria	37.2	27.3	19.1	15.1	5.5	5.5	0.8
Sardegna	43.2	19.5	19.5	14.2	7.0	4.7	1.0
Liguria	21.3	14.4	20.3	18.5	5.3	3.0	0.5
Marche	40.7	22.6	28.9	16.5	5.8	3,4	1.0
Abruzzo	40.3	24.9	25.8	15.2	7.1	4.5	0.7
Friuli Venezia Giulia	34.8	15.7	23.2	18.9	7.6	3.9	1,2
Trentino Alto Adige	34.6	14.4	15.6	12.3	5.9	3.3	0.9
Umbria	42.3	23.3	23.5	19.4	6.0	3.9	1.1
Basilicata	39.9	23.8	19.5	18.8	5.1	4.6	0.5
Molise	42.3	22.8	15.8	18.9	5.3	4.3	0.4
Val d'Aosta	27.7	15.9	19.6	13.3	5.3	2.6	0.8
M	36.0	20.7	20.6	16.3	5.7	4.1	0.8
SD	6.38	4.78	3.66	2.17	1.53	1.03	0.23
r Vs COVID-19 deaths	**-0.6551**	***-0.6459***	0.0011	***-0.4549***	0.0945	***-0.7693***	0.2243
r Vs Pneumonia Deaths	0.2971	***-0.7427***	***0.5448***	0.2194	-0.1109	***-0.7606***	***0.4961***

Table 4: DDD (defined daily dose) of some drugs: correlations with COVID-19 and common pneumonia deaths.

Statistically significant correlations ($p<0.05$) are reported in bold Italic characters.

Legenda: A = % of the population using the vaccine; H= Hormones (other than sexual hormones); J= Antimicrobial; S= Beta blockers and prostaglandin derivatives; L= Anticancer; D=Dermatological (topical anti psoriasis); P= Repellent pesticides.

Region	Density Inhab /Km^2	Flat land Inhab 10^6	Hills Inhab 10^6	Mountains Inhab 10^6	Rivers Km/km^2	Water Domestic/day L
Lombardia	422	4.71	1.24	4.06	0.068	321
Lazio	341	1.17	3.18	1.54	0.029	165
Campania	424	0.86	2.97	2.02	0.036	155
Sicilia	194	0.72	3.10	1.23	0.018	161
Veneto	267	2.77	0.71	1.43	0.058	160
Emilia Romagna	199	2.13	1.21	1.12	0.045	152
Piemonte	172	1.16	1.33	0.90	0.043	174
Puglia	206	2.17	1.84	0.06	0.012	133
Toscana	162	0.31	2.49	0.94	0.032	133
Calabria	128	0.18	0.97	0.82	0,006	221
Sardegna	68	0.30	1.12	0.22	0,022	158
Liguria	286	0.00	0.55	1.02	0.057	163
Marche	162	0.00	1,06	0.48	0.042	148
Abruzzo	121	0.00	0.46	0.86	0.043	167
Friuli Venezia Giulia	153	0.46	0.23	0.23	0.042	165
Trentino Alto Adige	79	0.00	0.00	0.00	0.049	162
Umbria	104	0.00	0.63	0.63	0.021	285
Basilicata	56	0.45	0.27	0.26	0.039	253
Molise	69	0.00	0.14	0.14	0.056	155
Val d'Aosta	39	0.00	0.00	0.13	0.026	185
M	182.6	0.849	1.175	0.955	0.0368	175.8
SD	114.17	1.2362	1.0312	0.9028	0.01679	47.53
r Vs COVID-19 deaths	***0.5355***	***0.4420***	-0.2950	***0.4744***	***0.5539***	***0.6391***
r Vs Pneumonia deaths	***0.6841***	0.1182	-0.2209	0.0364	0.4175	0.3420

Table 5: Demographic variables and water in the different Italian Regions: correlations with COVID-19 and pneumonia deaths.

Statistically significant correlations ($p<0.05$) are reported in bold italic characters.

Legenda: Inhab = Inhabitants; Rivers km/km^2 = Linear km in relation to the regional surface; Water Domestic/day L= Average daily consumption/ inhabitant.

Region	GDP € 10^3	Cars/1000 Inhab (2016)	Buses/1000 Inhab	Cell Use (2016)	Internet Connections % Inhab
Lombardia	38.84	1173	1.1	591	75.5
Lazio	33.58	633	2.0	594	74.6
Campania	18.59	580	1.9	598	70.5
Sicilia	17.68	635	1,5	569	66.9
Veneto	33.27	623	1.4	576	73.3
Emilia Romagna	39.29	631	1.4	555	73.8
Piemonte	31.49	656	1.4	555	70.1
Puglia	18.65	565	1.7	546	66.6
Toscana	31.54	655	1,5	633	71.2
Calabria	19.68	630	2.5	586	64.2
Sardegna	21.01	619	2.0	593	70.5
Liguria	32.25	532	1.6	534	71.9
Marche	28.08	653	1,8	476	75.2
Abruzzo	25.85	649	2,5	683	71.8
Friuli Venezia Giulia	31.36	642	1.3	455	70.0
Trentino Alto Adige	42.48	900	2.2	612	75.7
Umbria	25.29	701	2.0	449	69.4
Basilicata	21.87	641	3.4	456	66.0
Molise	20.65	667	3.7	425	66.0
Val d'Aosta	38.94	1170	2.7	400	67.7
M	20.370	697.8	1.96	555.3	70.7
SD	7.7118	176.66	0.689	76.04	16.17
r Vs COVID-19 deaths	***0.7745***	***0.5644***	***-0.4506***	0.0676	***0.6521***
r Vs Pneumonia deaths	***0.6820***	0.2376	***-0.6718***	-0.2615	***0.5942***

Table 6: Economic and life style variables in the different Italian regions in correlation to COVID-19 and pneumonia deaths.

Statistically significant correlations ($p<0.05$) are reported in bold italic characters.

Legenda: Inhab = Inhabitants; GDP = Gross Domestic Product; cell use = Minutes of conversation; Internet connection = % of families connected.

Discussion

The data reported in the present evaluation represent the trends of COVID-19 in the Italian Regions from 1st March to 4th May, at the moment of maximum lockdown.

The COVID-19 trends were compared to pneumonia to find similarities in relation to some of the most common chronic therapies and ecological, demographic/social and environmental variables.

The main limitation of this study is the use of correlations, which sometimes have a difficult, hidden interpretation.

The story of the correlation between babies and storks is a classical example. Storks are used to building their nests in warmer places and the houses where babies were born are usually warmer than all the other houses. This means that once a correlation between two events is significant, there must be a reason for it.

The COVID-19 trends

The number of positive cases was directly correlated with the number of swabs taken ($r= 0.8112$ $p< 0.01$), and the same was for deaths ($r = 0.7538$ $p< 0.01$). It is evident that all the curves may belong to the number of swabs. Hence, this makes it necessary to make a well-planned and homogeneous screening to establish a reliable comparison among the regions. In many instances, the swabs did not correspond to the true number of infected people because in some cases, subjects with a positive swab were used to repeat the analysis after a few days. Because of this, the number of deaths was considered a more solid variable.

The current opinion of virologists is that the number of positive cases represents between one-eighth to one-tenth of the total cases. This is an assumption that further complicates the interpretation of the data.

On 4th May, the swabs were performed in 943,151 subjects (1.56 % of the Italian population); 211,938 subjects were found symptomatic and unfortunately 29,079 people died.

Theoretically, the total confirmed positive cases in relation to 60.59 million of inhabitants will account for 0.35 % of the total population. In case the ratio 1/8th or 1/10th corresponds to reality, between 1.64 and 2.01 million people could be infected with the COVID-19 virus and theoretically with the ratio as 13.7 % of deaths, the total mortality will sum up to between 225 and 280 thousand people. It is very hard to believe these numbers correspond to reality.

A few days after the public information about the COVID-19 infection, most of the deaths in hospitals were attributed to this viral infection, although one should only consider those patients who really died of COVID-19, even though the distinction is not simple.

In a 2-month period of 2017 (the only public available data) the deaths for pneumonia, respiratory, infectious and ischemic heart diseases were 12,956 [23], while the deaths attributed to COVID-19 were in total 29,079.

Deducting from 29,079 the 12,956 theoretical deaths, the difference accounts for 16,123 cases in a period of 2 months. The death rate of COVID-19 during the lockdown was shown to be asymptotic, which means that from June up to the end of the year, approximately 3,500 more deaths could be expected. However, these figures did not take into consideration the possibility of another viral wave after the end of lockdown, when people would return to their normal activity.

The present figures have not exceeded those of the two previous dramatic events in 1956 and 2015, causing about 50,000 and 22,000 deaths in Italy respectively more than expected. The cause was attributed to a particularly cold winter and flu and also to an extremely hot summer.
The other historical dramatic event was during the Spanish flu in 1918, which caused 532,457 deaths within 8 months in Italy [26].

During the flu season 2018-2109 the estimated deaths were 205 only (26].

In the end, the expected deaths of COVID-19 should be about 80 times more than the normal flu, within the level of the episodes of 1956 and 2015 and several times less (about 25 times) than the Spanish flu.

The problem of swabs

The most common analysis for COVID-19 positivity is the nasopharyngeal swab, which needs one day for the test result (now quicker rapid tests can be used), while the much simpler and faster quick saliva test is now available.

Despite virus invasion of the parotid and other salivary glands [27], oral hygiene can hide the virus, making the saliva test temporarily negative (the same is for foods or drinks), with the consequence of giving many false negative test results. Usually, oral hygiene is carried out regularly in the morning. However, foods/drinks can be taken at any time of the day. This puts many doubts about the reliability of the saliva tests.

Because of this bias, our evaluation considered deaths as a more reliable variable, despite some interference (death with/ from COVID-19) or imprecision since death at home or in the nursing homes were sometimes not or partially reported.

The percentage between positive cases/deaths (13.7 %) is a very high figure and seems quite stable. It is much higher than in other countries, which is estimated around 4 % or even less. Probably this discrepancy seems to depend on the different evaluation of the causes of death (with or from COVID-19) and the efficiency of the given health-care system, but one may not rule out the possibility

of different virulence of the disease among different countries or different ethnical reactions to the virus.

The age and concomitant diseases

The impact of age and concomitant diseases has been already described [13, 28] with some controversial results. The Italian Health Authority describes deaths from COVID-19 as more common in a) elderly people (>70 yeas); b) people affected by chronic diseases; c) females who are less affected than males [13].

Age and death is a binomial very evident in nursing homes accounting for about 30 % of all deaths.
However, nursing homes should be considered as a "separate region", characterized by two peculiar variables: a) the feelings of abandonment and neglect; b) life in an age-segregated environment.

Based upon these data, there are governments that suggested a continuation of lockdown for people older than 65 years of age. The current results showed that there is no basis at all for this initiative. Quarantine is imposed on those tested positive, no matter their age, sex, chronic conditions or where you live (in a nursing home).

In comparison to the outcome of COVID-19-related death in chronic patients, no correlations were found among those with ischemic heart disease (as an example of CVDs), Alzheimer's disease (as an example of aging disease) and viral hepatitis (as an example of viral diseases. The only positive correlation was shown with cancers and infectious diseases. This is not in line with the assumption that chronic diseases represent a risk factor, which is the opposite for it looks like the therapy in place has a protective effect.

In conclusion, there is no connection about the relationship between age and chronic diseases with COVID-19 fatality.

Compared to COVID-19, the variables correlated with pneumonia showed a different pattern indicating COVID-19 as an independent disease.

The interference due to the concomitant therapies

Some of the therapies in place to treat certain diseases are shown to be protective, such as antimicrobial and topical steroids, which can be due to the control of potential superinfections or to the reduction of the inflammatory process typical of COVID-19 respectively.

However, the real cause of this favorable impact remains obscure and could be related only to a delay of the death. What is most probable is the protective effect of the seasonal flu vaccine. The natural immunity and/or the stimulated immunity induced by flu vaccination represent the defence which may counteract the viral growth up to a given exposition. A significant negative correlation between COVID-19 deaths and vaccination means that immunostimulants can help the natural defence.

How long does it take to reach the value of zero deaths?

The applied models [25] calculated during the lockdown measures showed that the trend for positive cases and death decay was asymptotic, starting in the middle of June and never reaching the value zero. This means that under such conditions the waves of COVID-19 have apparently a period of 6 months. However, the infection could start again when the lockdown is lifted and could easily overcome the asymptotic phase.

Furthermore, during the summer season because of the vacations the Italian people is moving (mainly South of Italy is a place for vacation) and asymptomatic cases can spread the virus in those regions where the infection was less present. This aspect makes almost impossible to calculate the real asymptote.

COVID-19: where does this virus come from?

The debate about the animal source in a wet market in Wuhan or from the labs of the same city is still ongoing, with very different views expressed. The hypothesis that during the infections among humans the virus mutates [12], may suggest that the COVID-19 infection in China (as atypical interstitial pneumonia) in the summer of 2019 was caused by a similar virus.

In relation to the "invasivity" and the "mortality" of the virus, two main different scenarios can be represented: a very invasive virus with a low mortality rate or a less invasive virus with high mortality rate.

The Italian scenario with a peak within 2-3 weeks from the start of the infection stands for a very invasive virus with a relatively limited death rate.

The debate was also very active to identify the country of origin of the virus.

China was apparently the first country where the virus appeared.

In Italy, the number of foreign residents in 2019 was 5,205,503, making up about 10 % of the population [29]. Significantly positive correlations were found between the percentage of deaths from COVID-19 in the Italian Regions and residents of foreign countries ($r = 0.5139$ $p< 0.05$;) [30], but this was not true for Romanians whose results did not correlate but was true for Peruvians, Filipinos and Indian residents. China showed a positive trend but not statistically significant. However, considering Lombardy as a separate Region (the most prosperous region and main industrial powerhouse in Italy), Chinese residents come out as the only positively correlated [30].

One hypothesis could be that in the most active and prosperous Italian Region, the presence of many ethnic groups might be an epiphenomenon of the industrial and agricultural activities. However, this is not true for Romanians.

Furthermore, one may consider that Chinese residents in Italy (particularly those residents in Lombardy), frequently travel to China. Italy is also a sought-after destination among Chinese tourists, especially fashion shoppers (in most of the provinces

of Lombardy) but not to the same extent as other residents (e.g. Peruvians, Filipinos).

Correlations of COVID-19 events with demographic, environmental variables

A positive correlation was shown between COVID-19 deaths and the population density, populations living in flat lands or mountains but not in the hills. The last aspect also includes factors like temperature, and humidity which have already been reported and discussed [1] the subsequent hypothesis is based upon the viral concentration in relation to the temperature and the ventilation of the respective territories. The common indexes of prosperity, such as GDP, cars, internet connection were found to be positively correlated, while the number of buses was negatively correlated (low density during public transportation).

A peculiar characteristic of COVID-19 is positively correlated with domestic water consumption. This variable was, however, not significant for pneumonia. The data exhibiting the domestic consumption of water were relative to the year 2011, but in the territories where the values were available, a very high correlation over time was shown ($r > 0.85$), which is with the solidity of this variable.

Rivers and water

Most of the rivers were considered (75 rivers), in terms of their length within the territory, without taking into account the water flow. However, the water flow is proportional to the river length. The smaller rivers (more than 200) are generated by the main rivers and the values obtained from the 75 rivers represent a reliable picture of the total number of rivers flowing in the regional territories.

Lakes were not considered and they are highly represented in the North of Italy. Despite most of them are generated by rivers, some lakes are not (e.g. Orte in Piemonte, Trasimeno in Umbria, Varano in Puglia). However, it was difficult to convert the area of the lake into linear km. In line with this, the additional km did not change the correlation (on the contrary, it was increased). Hence the positive relation between COVID-19 and rivers should be considered reliable.

Most of the time, the water of the river carries waste that is generated mainly by small and large factories. The lockdown (that started on March 8th), led to the reduced activity of these factories allowing the water to become clean and clear. Therefore, most of the pollution was not a consequence of domestic but mainly industrial use. In other terms, rivers should be considered a potential spreader for this virus. The concomitant correlation with domestic water consumption raises some important questions. Can the virus diffuse through the water? Does the temperature generated by the water influence the viral growth?

The high temperature may reduce the viral contamination [31], which is, however, not the case for water in rivers, lakes or in the houses. One possible explanation can be drawn from the viral structure.

The COVID-19 structure consists of 4 main sets of proteins: S (spikes), N (nucleocapsid), M (membrane) and E (envelope). The spikes mediate the viral cell-cell fusion with adjacent uninfected cells, forming giant syncytia that allow the spread of the virus. The E protein, despite being the smallest of the proteins, is important for viral spread because its loss determine the reduction of the viral population [32].

The E protein is hydrophobic and can protect the virus from water. A consistent temperature increase can modify this protein making it less effective, but this is not true regarding water at an average temperature, whether for domestic use or from the rivers/lakes.

The size of the COVID-19 virus ranges between 100-150 nm and the filtering devices for domestic water can stop particles up to 20,000 nm. Thus, they are inadequate to stop the virus from contaminating domestic water supplies. An efficient water purification system usually eliminates the virus load, either by filtration or by physico-chemical treatment (e.g UV, chloride, NaClO). However, contamination can take place once the water gets into the pipelines of the respective regions and houses.

The household water consumption can also be an epiphenomenon of the status of well-being, meaning that the amount of water consumption represents a lifestyle habit. However, higher water consumption leads to more evaporation and the spread of contaminants within the evaporating particles.

As a result of this, the direct/indirect effects of water should be considered. However, appropriate studies and controls have to be carried out. Additionally, one should take into account that the major Industrial areas of Italy have ample water resources that can be considered as a consistent prosperity index.

Economic and social variables

Positive correlations were significant with those variables that are associated with a high status of well- being, which are represented by the GDP, cars and internet connection. In a previous study, the number of industries/workers was found to be positively correlated that was consistent with a higher frequency of interrelations among people [1].

No correlation was found pertaining to mobile data traffic, which represented interconnections without direct contact. Comparing COVID-19 deaths with those of pneumonia, it was evident that COVID-19 was behaving differently.

Correlations with drugs

The aim of this analysis was to determine if there are drugs that could prevent or lead to an increase in the COVID-19 death rates.

Here the limitation of this variable is that the records are related to drug classifications, which sometimes are composed by more than one molecule. In this case the comparison was also done with deaths for pneumonia.

None of the drug categories were positively correlated with COVID-19 deaths. However, most of them were negatively correlated indicating that chronic therapies seem to be protective. The number of vaccinations during 2018/2019 [33] was negatively correlated and could be helpful, even though they were not specific for COVID-19. This shows that the chronic therapies and vaccines appear to increase the survival rates.

Hence, deaths related to COVID-19 are multifactorial and therefore treating one or more of these factors (e.g. inflammation, coagulation) might possibly reduce the number of deaths.

Currently, several clinical trials exist that study treatment options for COVID-19 (e.g. antimalarial, antiviral, monoclonal antibodies, steroids, antithrombotics and anti-inflammatory agents). The EU Clinical Trials Register reported on May 2020 [34] that 95 clinical trials (one center or multicenter) are currently assessing COVID-19 treatment possibilities. However, these trials only account for the officially registered number as many additional clinical investigations without registrations are conducted, too. Nonetheless, the present results of antiviral therapies are controversial.

The future with COVID-19

Current infections can be caused by more than one viral strain of COVID-19 as the extremely high number of cases show that some new mutations are involved too.

This viral cycle is expected to last for around 6 months. This is not the case for the other seasonal flus whose cycle lasts much shorter. After reaching the peak values, the curves of positive cases and deaths decreased with an asymptotic shape, even though the projections up to the value zero cannot be determined properly. Furthermore, one may not exclude that the infection will start again once the lockdown has ended.

The aggressiveness of the virus accompanied by the high number of asymptomatic subjects indicate that COVID-19 is most likely already part of the human meta-organism.

As seen with AIDS and some hepatitis virus infections, humans have to cohabit with this particular virus too. It is likely that every forthcoming year will be rather similar, with the only difference that our doctors will be skilled to deal with the disease.

Conclusions

There are 7,904 Italian Municipalities with a total population of approximately 60.6 million inhabitants.

Within less than 2 months, a number of citizens corresponding to approximately four municipalities died.

This event was about 80 times more severe than the seasonal flu, similar to the flu that appeared in Italy in 1956 and 2015. It is less dramatic than the Spanish flu in 1918 during World War 1 when Italy was in a state of misery.

Nowadays, the situation is different. COVID-19 hits a country characterized by high economic and social progress and targeted the most developed Italian territories. The effects were particularly severe in the flat, industrial, prosperous regions with water abundance and a very active way of life. The life cycle of this COVID-19 wave lasted about six months, quenched by a lockdown which unfortunately created extremely high social and economic problems.

Despite common beliefs, the age and concomitant diseases of the patients do not seem to increase the death rate. Chronic therapies and non-specific flu vaccinations were found to limit COVID-19 mortality.

However, one should not exclude the possibility of COVID-19 reactivation as soon as the country will return to its normality. This means that masks have to be worn and the excessive gathering of people should be avoided. Lastly, our lifestyle needs to be modified accordingly.

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UC conceived the trial; UC, GB, MRC, RC were collecting the data; MR was in charge to make the statistical evaluation, UC wrote the text.

Ethical statement

The manuscript is original, has not been published before and is not being considered for publication elsewhere. All the authors mentioned in the manuscript have agreed on the authorship, read and approved the manuscript, and given consent for submission and subsequent publication for the manuscript.

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