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Commentary

Parallel epidemics, or nearly so: Certainties and uncertainties about SARS-CoV-2 in Italy

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Between the end of the second and the beginning of the following century BC, the Greek philosopher Plutarch wrote "The parallel lives", a series of twin biographies, each of which comparing a Greek and Roman prominent figure as for life events, vices and virtues. Now that our world is facing SARS-CoV-2 pandemics with its relevant country-specific timing and evolution pattern characteristics, we feel like repeating Plutarch's parallelism experiment by analyzing factors eventually influencing its expression in different and far afield countries and by trying a head-to-head comparison between two main Italian regions.

The history of COVID-19 pandemics is contributed to by a series of events occurring between the end of 2019 and the beginning of 2020 caused by SARS-CoV-2 virus infection, starting in Wuhan, China, and spreading throughout the world thereafter [1,2].

Event sequence

The first COVID-19 infection case, referring to a 55-year-old man in Hubei province, was recorded on November 17, 2019 [1,2]. In the very beginning the agent was not identified as a new type of coronavirus, so that the news was reported by the Chinese government only on January 13, 2020 [3]. Immediately after the epidemics became apparent so that Hubei province and the town of Wuhan were isolated and some 60 million people underwent a strict, army-secured quarantine which guaranteed the outbreak switch-off in about two months.

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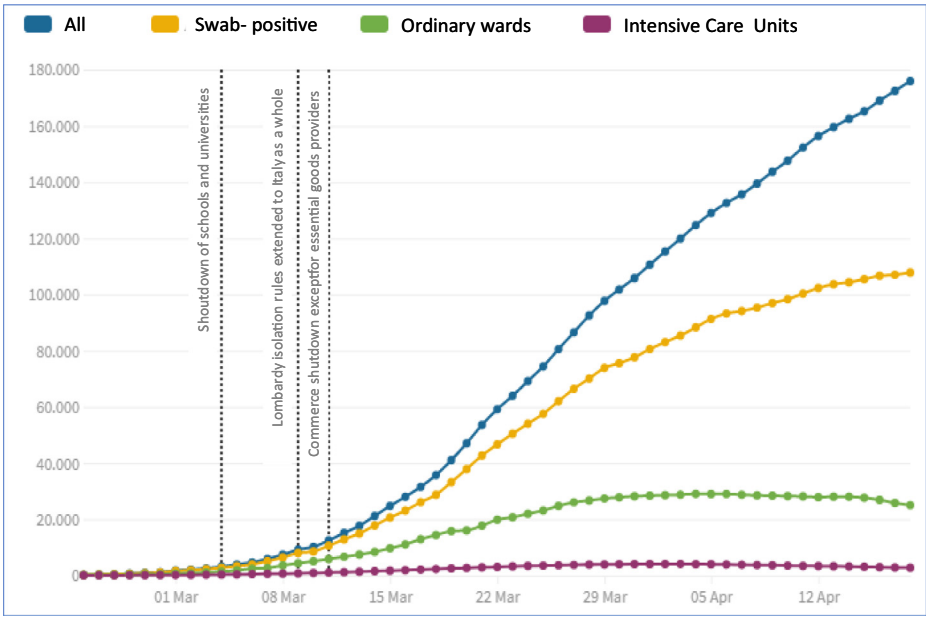


Fig. 1 – Overall trend of the epidemic in Italy as of April 18, 2020 with respect to progressive Governmental restrictions (Source: Date from the Ministry of Health processed by the ISS, modified) [10]

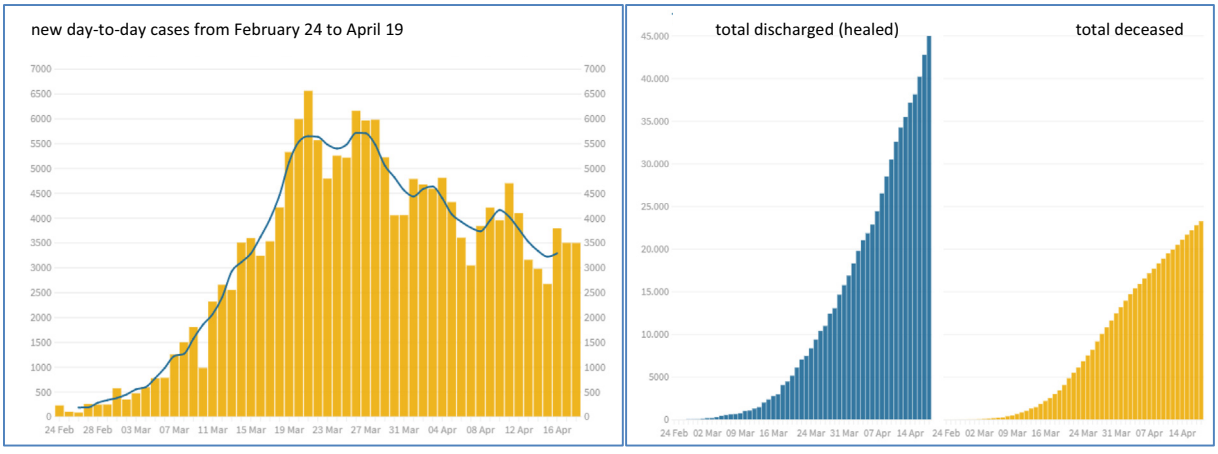


Fig. 2 – New day-to-day (in yellow) SARS-CoV-2 swab-positive patients (left panel), death cases (right panel) and moving average of healed individuals on a continuous 5-day basis (middle panel, in blue) as of April 18, 2020 (Source: Data from the Ministry of Health processed by the ISS, modified). [10] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3 – Admission trends to ICUs (left panel; the arrow shows the peak level reached on April 3) and ordinary wards (right panel; the March 29 arrow shows the 29,010 individual peak level) (Source: Sky TG 24 on data from the Ministry of Health processed by the ISS, modified) [11].

Italy recorded its first COVID-19 pandemic event on January 31, 2020, when two tourists coming from China were found to be virus-positive in Rome [4]. On February 20, new outbreaks were detected in Codogno, Lodi province, Lombardy region, in terms of 16 infected people, summing up to 60 on the following day and causing the first deaths soon after [5–8]. The patient identified as Case 1 was a 38-year old man from Codogno having respiratory tract infection signs. His wife and a close friend were also found COVID-19-positive [5] so that 13 municipalities in Lombardy and one in Veneto were immediately isolated to fulfil contagion containment procedures [9]. Figs. 1–3 depict the evolution pattern of the epidemic in Italy throughout April 18, 2020 showing some slight positive signals, despite an overall long-lasting trend.

When referring to the initial cases recorded in Lazio and in Lombardy, the epidemic has consistently followed parallel trends in the North (quite turbulent) and in the Center-South of Italy (much slower) and now, when freezing the official picture derived from data of the Ministry of Health processed by the Istituto Superiore di Sanità (ISS) as of April 18, 2020 (Table 1), we detect a huge difference between the two regions. Demographic data is quite different and strongly in favor of Lombardy in terms of number of provinces, municipalities, inhabitants, geographical surface and population density (people/km^2) [12]. In greater detail, when looking at results from the two regional capitals, accounting *per se* for the highest population density and consequently most relevant contagion spread risk, a paradox becomes immediately apparent: despite having fewer inhabitants than Rome (1,352,000 versus 2,873,000), Milan has suffered from a five-fold infection rate so far (see Table 2).

Which reason might underly such a clear difference?

Despite discrepancies in timing, modality and rule severity, China and Italy adopted similar containment procedures, yet the spread of contagion was much faster in Northern than in Southern Italy (almost invariably comparable to Lazio). It is quite evident from Wuhan experience that the stricter the isolation rules for assessed or potentially infected people, the easier it is to prevent SARS-CoV-2 spreading. This was the case in Rome where, immediately after being diagnosed, the two Chinese infected persons were admitted into the Spallanzani Hospital, a 40-year-renowned research and care center for infectious diseases and all their travel-mates and contacts were identified and isolated into the Cecchignola military citadel on the outskirts of Rome. All over Lombardy, instead, due to the lack of symptoms of infected people for several days or even weeks, virus spread was much wider, thus reaching out to Veneto and Emilia-Romagna regions, and presumably required longer to develop earlier symptoms after being infected.

This might be explained by the fact that the two Chinese cases in Rome were older than Case 1 in Codogno (i.e. 68 vs 38 years of age). The former followed an easily traceable tourist itinerary while the latter moved around quite easily and extensively among regions making it impossible to track

Table 1 – Absolute number of SARS-CoV-2 infected individuals as of April 18, 2020 in Lombardy compared to Lazio. (Source: Data from the Ministry of Health processed by the ISS, modified). [10]

LOMBARDY	
TOWN	CASES
Bergamo	10,629
Brescia	11,758
Como	2,439
Cremona	5,407
Lecco	2,03
Lodi	2,714
Monza Brianza	4,042
Milan	15,546
Mantova	2,863
Pavia	3,536
Sondrio	937
Varese	2,106
other / to be verified	1,374
TOTAL	65,381
LAZIO	
TOWN	CASES
Rome	4,018
Frosinone	505
Rieti	280
Viterbo	349
Latina	436
other / to be verified	80
TOTAL	5,668

Table 3 – Absolute and relative prevalence of most common pre-existing cardiovascular and metabolic comorbidities as retrieved from available charts concerning 1,890 COVID-19-positive people dying in Italian hospitals. [21].

Disease	N	%
Ischemic heart disease	518	27.4
Atrial Fibrillation	411	21.7
Heart failure	298	15.8
Stroke	206	10.9
Hypertension	1,317	69.7
Type 2-Diabetes	603	31.9
Obesity	230	12.2

Table 2 – Demographics from Lombardy and Lazio. (Source: Statistics from ISTAT - Istituto Nazionale di Statistica). [13].

Region	population inhabitants	surface km^2	density inhabitants/km^2	number of municipalities	number of provinces
Lombardy	10,060.574	23,863.65	422	1,506	12
Lazio	5,879.082	17,232.29	341	378	5

down all contacts. Moreover, the evidence so far seems to indicate that, besides being burdened by higher mortality due to the frequent coexistence of other diseases, older subjects are more easily infected and severely ill and this might have caused weakness symptoms quite soon preventing the Chinese patients in Rome from moving around [13,14]. There are also anecdotical reports concerning a shorter incubation period in the elderly which might add to the above, yet further studies are still needed to validate such hypothesis.

Are there any other possible explanations for accelerated coronavirus spread in Lombardy? Indeed, the most affected area in the region, including Milan and its hinterland, is quite rich in farms and industries asking for intensive daily commuting and in the early phases of the epidemic most activities were still in place and partially stopped only about two weeks later. In fact, beginning of March, after the outbreak had already shown its threatening potential, only "crucial" activities were allowed to go on including food and drug chains, logistic support providers, general practitioner (GP) offices, which anyway involved some 40% of the working population [14]. So considerable train, metro and bus commuting, relatively late recognition and multiple outbreak sites might have favored such a large infection spreading pattern in Northern Italy.

Two more observations might also be taken into account, albeit requiring further validation by controlled studies: (i) a large number of treatment-resistant pneumonia events occurring already in January were reported by GPs *a posteriori*, i.e. after SARS-CoV-2 outbreak, and might reflect the presence in the area of potentially unrecognized carriers responsible for the exponential spreading of coronavirus infection [15] and (ii) more severe fine dust pollution and less favorable hygrometric and barometric environmental conditions characterize the whole Po Valley as compared to the rest of Italy, as also apparent from European Space Agency reports [17,18].

Finally, as far as type 2 diabetes mellitus (T2DM) is concerned, we now have to underline that, as recently pointed out by two Italian groups [15,19] and reported by Chinese scientists directly involved in the management of COVID-19 infection [20,21], the disease is extremely frequent and associates with a higher mortality rate in hospitalized patients (Table 3) [22]. Such phenomenon, which was further confirmed in Italian patients by the most recent bulletin from the ISS, had become apparent, despite different prevalence estimates, since the very beginning of the epidemic in China [15].

Diabetes and uncontrolled glycaemia had already been reported as significant predictors of severity and deaths in patients infected with different viruses as well, including the 2009 pandemic influenza A (H1N1) [23], SARS-CoV [24] and MERS-CoV [25].

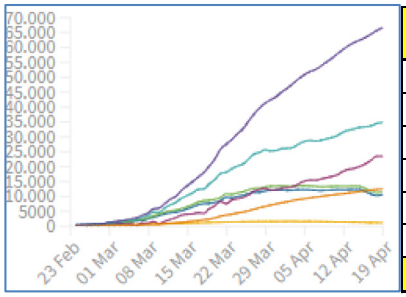
SARS-CoV-2 Infection in individuals with DM is expected to trigger higher stress conditions, with greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability [26]. On the other hand, according to a retrospective study from Wuhan some 10% COVID-19-positive patients with T2DM suffered at least one hypoglycemic event (<3.9 mmol/L) [27]. Notoriously, hypoglycemia mobilizes pro-inflammatory monocytes and increases platelet reactivity, thus contributing to a higher cardiovascular mortality in patients with DM [28].

In addition, hyperglycemia and insulin resistance enhance the build-up of glycosylation end products (AGEs) and pro-inflammatory cytokines causing severe oxidative stress and increased inflammation-related adhesion molecule release [29–31]. All this may in fact contribute to the mechanisms underlying the greater susceptibility to infections and the worse outcomes thereof observed in patients with DM [30].

Mostly based on *in vitro* studies, hyperglycemia associates with several immune system defects, including inhibited lymphocyte proliferative response to different kinds of stimuli [32,33], and impaired monocyte/macrophage and neutrophil functions [30]. *In vitro* studies have shown that pulmonary epithelial cells exposure to high glucose concentrations significantly increases influenza virus infection and replication, pointing to hyperglycemia-enhanced viral replication *in vivo* [34]. In animal models, structural lung changes have been related to diabetes, such as augmented vasculature permeability and collapsed alveolar epithelium [35]. Finally, abnormal delayed-type hypersensitivity reaction and complement activation dysfunction [36] have been reported in patients with DM. All of the above suggests that the greatest possible attention should be paid to the high risk for more severe lung involvement pending on people with DM during COVID-19 infection, due to a significantly lower forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in the presence of raised glucose levels [37].

So which pathogenetic elements underly higher susceptibility to COVID-19 disease and mortality rate in people with DM? The virus itself and its toxins precipitate a cytokine thunderstorm exacerbating hypercoagulation in patients with DM [20,34] who, by definition, face a clear-cut prothrombotic state [35], further aggravated by chronic low-grade inflammation causing atherosclerosis-related endothelial dysfunction and insulin-resistance associated arterial hypertension [36]. All above-mentioned phenomena are known to become more and more severe as age increases and this is in line with the observation that octogenarian individuals are mostly affected by SARS-CoV-2 disease [19].

With respect to that, an issue deserving special attention is the quite similar SASR-CoV-2 infection rate in people without or with DM [25] in front of a much greater severity of the disease as reported by the Italian ISS in the latter. At this point we also feel like underlining that some hypoglycemic treatment strategies might turn out to be protective. Dipeptidyl-dipeptidase-4 (DPP-4) was shown, in fact, to be the primary receptor of MERS-CoV [37]: the possibility that DPP-4 also acts as a receptor for SARS-CoV-2 warrants investigation and, should this be the case, in agreement with the hypothesis put forward by Iacobellis [38], DPP-4 inhibitors, well-renowned treatment tools in T2DM, should be explored for their anti-viral potential in the human [15]. Opposite to that, it has been recently hypothesized that Sodium-Glucose-Transporter-2 inhibitors (SGLT-2i), Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1RAs), Pioglitazone and even Insulin might induce an over-expression of the ACE2 receptor which was also found to bind to coronaviruses in the alveoli [39], and therefore increase the risk for a more severe expression of SARS-CoV-2 infection in people with diabetes [40].



Patient groups		Lombardy - n (%)	Lazio - n (%)
Admmitted to ordinary wards	(dark blue)	10,042 (15.9%)	1,314 (25.1%)
Admitted to ICUs	(yellow)	922 (1.5%)	187 (3.6)
Hospitalized as a whole	(light green)	13,200 (20.9%)	1,519 (29.3%)
Isolated at home	(violet)	21,286	2,695
Swab positive	(dark green)	28,124	4,144
Deceased	(orange)	10,904 (17.2%)	300 (5.7%)
Total	(black)	63,094	5,232

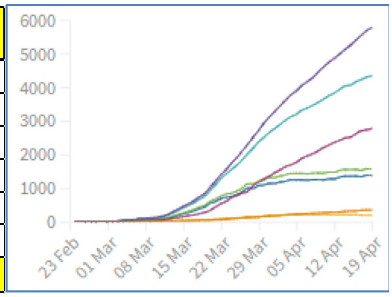


Fig. 4 – Patterns of the epidemic in Lombardy (left panel) and Lazio (right panel). Legends in the middle. (Sky TG 24 https://tg24.sky.it/cronaca/approfondimenti/foto/numero-contagi-coronavirus-italia.html#4: data from the Ministry of Health processed by the ISS, https://www.iss.it/coronavirus) [12].

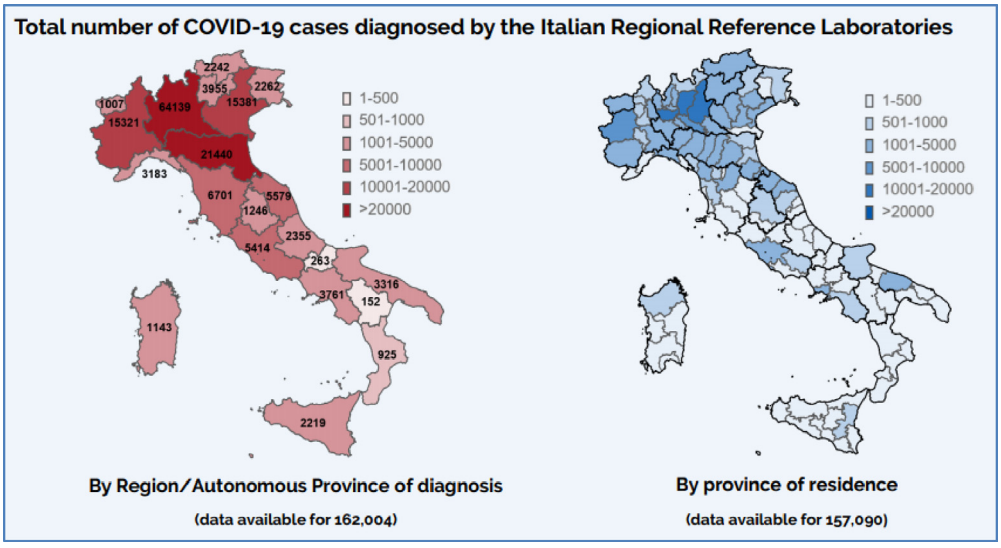


Fig. 5 – Territorial differences in SARS-CoV-2 infection within Italy as of April 16, 2020 (Source: Data from the Ministry of Health processed by the ISS, modified) [16].

Corticosteroid utilization also requires special attention with respect to COVID-19 disease severity in people with DM [41]. Acute lung damage and acute respiratory distress syndrome (ARDS) are partly due to the host immune response and corticosteroids were broadly used in SARS-CoV and MERS-CoV infections [42,43] due to their ability to suppress histologically proven virus-dependent lung inflammation with diffuse alveolar damage [44]. However, they also inhibit immunity and pathogen clearance and, in the face of very little benefit if so ever, have been associated with delayed viral RNA clearance or increased mortality and rate of complications, including diabetes, psychosis, and avascular necrosis [42]. Due to all the above, the interim guidance from the WHO on clinical management of severe acute respiratory infection advises against the use of corticosteroids upon suspicion of SARS-CoV-2 infection outside clinical trials [45], yet corticosteroids were extensively utilized before that in at least 34% of the large number of Northern Italian hospitalized patients [46]. At analysing the growth curve of coronavirus infection in Italy, the massive referral to the hospitals of so many people within a very a short period strikes the eye when compared to the small number of hospitalized patients in the South (Figura 4). In the stormy and overcrowded emergency conditions faced by health professionals at the start of the epidemic in the absence of any experience with treating COVID-19 disease, a broader recourse to high doses of corticosteroids most likely occurred than later on, when in fact better treatment strategies were identified and emergency departments were less congested. It can be assumed that the above mentioned logistic and environmental factors strongly affected clinical course and mortality rates of COVID-19-infected people and even more in those with DM. Indeed, Fig. 4 clearly shows that death rate was significantly higher in infected Northern Italy inhabitants than in their Southern counterpart (i.e. 17.2% vs 5.5%, respectively). According to current protocols, subject to the exceptions needed for treatment personalization, the use of corticosteroids is extremely limited if so ever. This might also help healthcare teams adopt an intensive, fully integrated therapeutic approach for their patients with DM, especially those in the ICUs, involving drugs expected to prevent at their best both hypoglycemic events and dramatic hyperglycemic spikes contributing to marked glycemic variability, i.e. a severe mortality risk driver [47] (see Fig. 5).

A final report coming from TOSCA, a recent nationwide study on people with T2DM, known to affect mostly older patients who, in turn, are at higher risk for severe COVID-19 disease, shows that a high adherence to the Mediterranean diet is significantly more frequent among people living in the southern regions of Italy [48]. The latter, however, display a slightly higher phenolic acid and lignan intake due to a higher consumption of cereals and legumes and a slightly lower total polyphenol intake as flavonoids and stilbenes due to lower wine consumption [49]. This takes on a particular significance when comparing the absolute and relative death rate of subjects with T2DM in Lombardy (11,384 deaths; 56.9% of infected individuals) to that observed in Lazio (259 deaths; 1.3% of infected individuals). Might this add to the picture? At the moment, ours can only be taken as speculation but we strongly believe that also lifestyle components deserve further investigation with respect to COVID-19 disease.

In conclusion, based on official Ministry of Health and ISS statements we are fully aware that:

- a strikingly different trend was observed for SARS-CoV-2 infection between Northern and Southern Italy;
- strict containment rules are the best way to prevent SARS-CoV-2 epidemics from spreading;
- territory-oriented medicine might play an effective guardian role and should therefore be listened to and strengthened;
- people with T2DM are more susceptible to SARS-CoV-2 infection, with twice as high mortality risk as metabolically healthy people;
- high amounts of polyphenol-derived antioxidants from cereals and legumes typical of the Mediterranean diet might help to stop SARS-CoV-2 infection from spreading.

To borrow from Plutarch, the conditions described above are asymmetrically parallel. So, asymmetry proved to be detrimental to Italy, and especially its Northern part and to somewhat spare the Central and Southern areas so far, whose ancient Greek culture-derived lifestyle might have positively, albeit almost unexplainedly and inadvertently, influenced the susceptibility to coronavirus infection.

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All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and that it will not be published elsewhere in the same form, in English or in any other language, including electronically, and have given their approval for this version to be published.

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Ours was a spontaneous, unconditioned study.

Ethical standard:

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as revised in 2013.

Human and animal rights:

This article does not directly use experimental data on humans or animals, but reports data derived from the literature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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