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By Dr. Giannotta Girolamo & Giannotta Nicola

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Findings: The number of total cases increased by about 40 times in the period 2-20 March (from 2,036 to 80,539). In the same period, the active cases increased by about 21 times (from 1,835 to 37,860). Active cases do not close quickly and remain open for a long time because those who enter in intensive care do not recover before 2-3 weeks. On March 19 Italy's death toll surpasses China's, becoming the country with the highest number of coronavirus deaths in the world. On March 26 the deaths in Italy are more than the double of those of China (8,215 deaths in Italy, vis 3,287 deaths in China).

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Conclusion: Poor management of medium cases, in accordance with WHO guidelines, inevitably leads to overload of intensive care units. The progression of clusters in Southern Italy is more pronounced in Campania, Puglia and Sicily. The main cause of the high mortality would be attributable to the partial collapse of the Italian health system.

I. Introduction

In December 2019, an epidemic started in China caused by a new coronavirus (SARS-CoV-2), probably derived from bats. Severe acute respiratory syndrome-coronavirus (SARS-CoV) enters the human cells expressing the ACE2 receptor which is a transmembrane protein with its catalytic site located outside the cell [1]. ACE2 receptors are expressed in various human tissues, including lung and brain [2]. COVID-19 disease is caused by SARS-CoV-2 and has a certain degree of lethality. Although the main cause of death from COVID-19 is severe pneumonia, which often leads to acute respiratory distress syndrome (ARDS), which requires hospitalization in an intensive care unit, the virus is neurotropic and the brain of patients affected from COVID-19 can become infected [3]. It has been shown that in brain sections from SARS patients, the virus was detected almost exclusively in neurons [4, 5]. In addition, human neurons express ACE2 receptors [6]. In studies conducted in mice it has been seen that the virus enters the brain via the olfactory bulb and can cause extensive neuronal infection which can lead to death due to damage of neurons located in cardiorespiratory centers [3]. Furthermore, during the Chinese epidemic from COVID-19 it has been shown that some subjects could have an impairment of the cardiorespiratory centers and that the virus could access the central nervous system through the synaptic connections of the mechanoreceptors and chemoreceptors of the lung and lower airways [7]. In Italy mortality is very high and cannot be justified by a different ACE2 expression, even if ACE2 expression increases with age [8].

In this paper, we presented a series of data relating to the Italian epidemic, and we analyzed some trends. Furthermore, we have identified and listed a series of mistakes and risks related to a not perfect management of the recent epidemic which is still in full evolution. In addition, we compared the four epidemic management models implemented by the UK, China, Italy and South Korea. They are management models that have critical points, and that deserve careful analysis.

II. Materials and Methods

We have collected and analyzed the data produced daily by the Civil Protection. We cataloged this data and produced tables and graphs to obtain dynamic curves for certain parameters. In addition, we also calculated the change in active cases with the following formula: (newly infected) - (new deaths) - (new recoveries).

III. Results

a) Progression of total cases

The total number of cases in the period between 2 and 8 March have more than tripled. In the period between 8 and 14 March the number of cases have still tripled, but they are 10 times those that have been registered on the 2nd March. In the period between 14 and 20 March, the total number of cases have more than doubled, and the number of cases that have been registered was 23 times the number of cases registered on 2 March. In the period between 14 and 20 March, the number of total cases went from 47,021 to 80,539 (Fig. 1). This number is about 40 times that of March 2nd.

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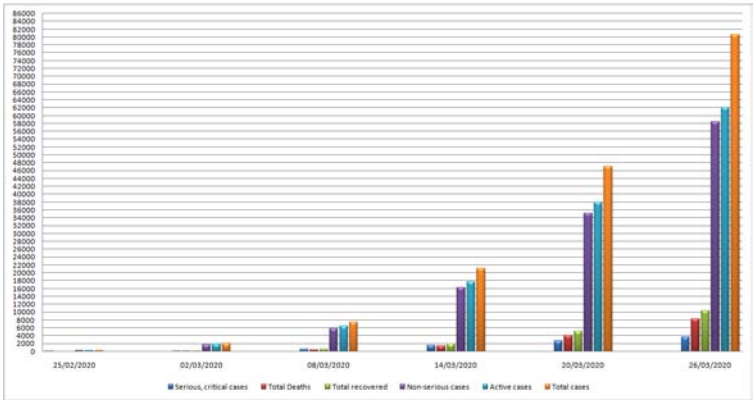


Figure 1: Progression of total cases.

b) Distribution of active cases

Active cases tripled in the period between 2 and 8 March, still tripled in the period between 8 and 14 March (but 9 times the cases registered on March 2). The value of active cases doubled (18,000 vis 38,000) in the period March between 14 and 20 (19 times the value of March 2). In the period between March 20 and 26, the active cases went from 37,860 to 62,013 (Fig. 2).

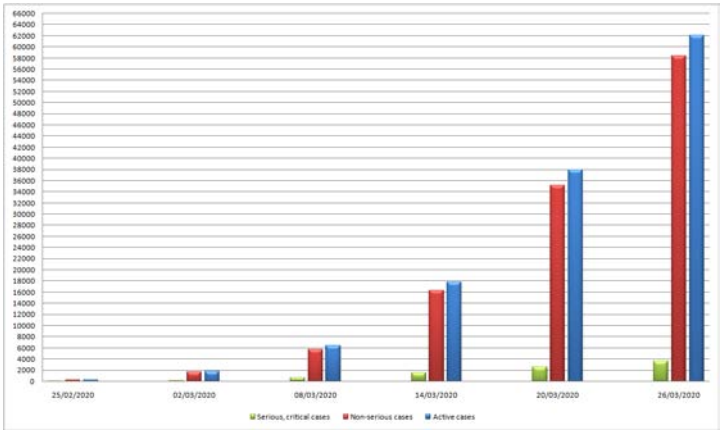


Figure 2: Distribution of active cases between serious / critical cases, and non-serious cases.

c) Change in active cases

Active cases grow consistently over time (Fig. 3). The new deaths and the new recovered become closed cases and leave the active cases. Only the new infected can enhance the curve, but they are too few compared to the total number of active cases and this, in our opinion, means that active cases do not close early and last long in the open case condition. In other words, an infected person who develops a medium to severe disease does not recover soon, probably not earlier than 2-3 weeks. Therefore, every serious subject who ends up in the intensive and / or sub-intensive care units remains there long before reaching clinical recovery.

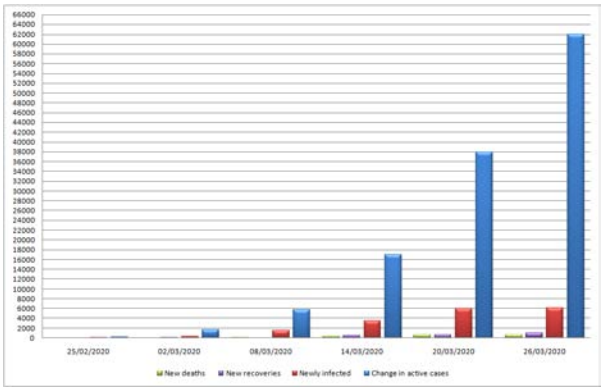


Figure 3: Change in active cases.

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d) Clusters in Southern Italy

The progression of clusters in Southern Italy is more pronounced in Campania, Puglia and Sicily (Fig. 4). Since the great exodus of people coming from the Northern and going to the Southern Italy occurred on March 7, and a similar exodus, but of smaller proportions occurred on March 14, it is still early to verify if the "measures of social distancing", suggested by the Italian government, have produced effects in terms of slowing the spread of the infection down.

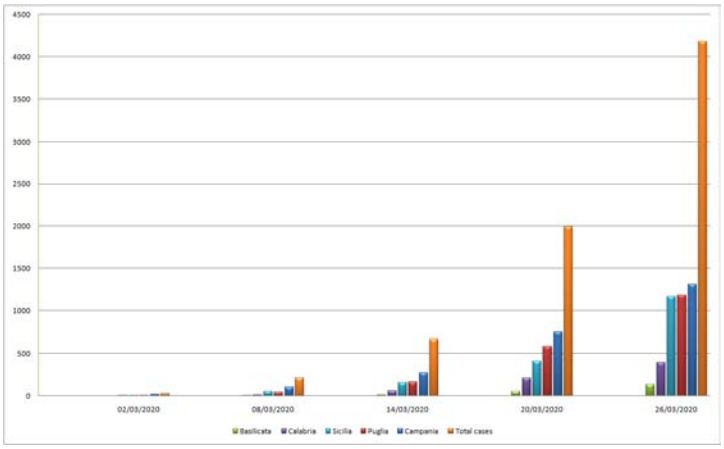


Figure 4: Clusters in Southern Italy.

IV. Discussion

Before describing the characteristics of the Italian epidemic, we will describe the characteristics of four different management models. There are four different models that have been used to combat the COVID-19 epidemic. On our point of view, at present, the model that has been proven most effective is the one used by South Korea, followed by the Chinese totalitarian model. The other two models, the Italian and the English ones, are bad models not to be used in other countries, due to the critical issues they present, and which we will explain.

a) South Korean management

South Korea has been able to slow the progression of the epidemic down. In fact, on March 26, there were 9,241 total cases with 131 deaths, 4,144 recovered, 4,966 active cases, and 59 serious cases. They used a large testing program (tested more than 270,000 people) and they were able to isolate infected people and track contacts in order to quarantine them. New legislation has made it possible to overcome the limitations imposed by privacy laws (which exist in democracies) by giving health authorities the opportunity to reconstruct the movements of test positive subjects. Then, particular applications managed on social media allowed individual subjects to check whether they had contact with infected people [9].

b) Chinese totalitarian model

The military closure of the province of Hubei, the isolation of Wuhan city, the identification of cases and contacts, their mandatory quarantine and the environmental remediation systems in order to prevent the non-human spread, have made it possible to control the epidemic in about 4 months.

c) The English model: Herd Immunity or Herd Mortality?

English prime minister's initial idea, supported by a team of scientists, was to not take any measure to contain the SARS-CoV-2 infection. This was not only a serious political mistake compared to a pandemic, but above all it was a defeat of science. In fact, only children have a great number of natural killer (NK) lymphocytes with adequate cytotoxic capacity, and with an ability to kill cells infected by the virus [10], without a preliminary presentation of foreign proteins by antigen-presenting cells (APC). In addition, these lymphocytes produce several cytokines that regulate the immune system [11], and the NK lymphocytes have immunological memory, like the T- and B-lymphocytes [12].

On march 22, 2020, the citizens of the UK gave a bad test of the perception of the danger, invading beaches and public parks. On march 23, UK Prime Minister Boris Johnson has announced that the country will go into a complete lockdown: Britons will be allowed to leave home only if essential.

d) The Italian model: quarantine with continuous spillover

On February 19, the deaths in Italy exceeded those in China, even though the total number of positivity to the SARS-CoV-2 in Italy was about a half of the ones in China. This unusual virulence at the moment has no plausible explanations and we do not know if it can be related to the characteristics of the coronaviruses circulating in Italy and / or to certain characteristics of the people affected by COVID-19. However, on March 26 the deaths in Italy are more than the double of those in China (8,215 deaths in Italy, vis 3,287 deaths in China).

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e) Clusters in Southern Italy

On March 8, a decree law is produced by the Italian government that limits traveling on Italian territory, but this announcement is made on the mass media one day before the publication of the same decree. This announcement completes a mass exodus towards Southern Italy that would have brought more than 100,000 citizens out of the Regions with the highest viral transmission. These citizens arrived at their destination on March 8 when in the 5 Regions of Southern Italy there were only 207 cases of test positivity for SARS-CoV-2 (Tab. 1).

Table 1: Total number of test positivity for SARS-CoV-2.

Region	2 Mar	8 Mar	14 Mar	20 Mar	26 Mar	1 Apr
Campania	17	101	272	749	1,310	2,231
Puglia	4	40	166	581	1,182	1,946
Basilicata	0	4	10	52	134	237
Calabria	1	9	60	207	393	669
Sicilia	7	53	156	408	1,164	1,718
Total cases	**29**	**207**	**664**	**1,997**	**4,183**	**6,801**

On March 26 there are 4,183 test positivity for SARS-CoV-2 (about 20 times, compared to the cases of March 8). This spillover changes the epidemiology and all the prediction models of the Italian epidemic trend, because it inserts a new variable, which on the one hand, leads to the expansion of the viral transmission, and on the other it shortens the duration times of epidemic, because it increases the number of citizens infected by unit of time, and the territories affected by the same viral transmission. In fact, a prediction model of the estimate of the number of patients [13] who could be affected as of March 15, led to an error in the estimate of about 23% (estimated about 32,000 infected patients, vis really infected 24,747).

According to ISTAT data, updated to January 1, 2019, the population of Southern Italy was represented by over 17 million inhabitants [14]. Based on population density, Campania is at a higher risk of spreading the infection, while the risk of spreading is halved in Puglia and then decreases in other Regions, as indicated in table 2. If the positive cases identification measures will work (number of tests), and contacts will be traced and placed in quarantine, the supplementary measures of "social distancing" will slow down the spread of the infection.

However, on March 26, the size of the clusters of Campania differ for a little from those of Puglia (1,310 vis 1,182) and this could be a bad sign for Puglia (Tab. 1).

Table 2: Population and inhabitants density in Southern Italy.

Region	Population	Density Inhabitants / Km^2
Lombardia	10,060,574	422
Campania	5,801,692	424
Puglia	4,029,053	206
Sicilia	4,999,891	194
Calabria	1,947,131	128
Basilicata	562,869	56
Total Inhabitants In Southern Italy	**17,340,636**	

f) Higher mortality than other countries

The Istituto Superiore di Sanità (ISS) states that mortality in persons with confirmed COVID-19, in the Italian population, as of March 17, was 7.2%, much higher than in China (2.3%), and still higher than the one observed in other countries. The fatality rate was defined as number of deaths in persons who tested positive for SARS-CoV-2 divided by number of SARS-CoV-2 cases [15], but the resulting number does not represent the true case fatality rate (CFR) and might be off by orders of magnitude.

However, two facts remain:

1. On March 19 Italy's death toll surpasses China's, becoming the country with the highest number of coronavirus deaths in the world;
2. On March 26 the dead in Italy are more than double those of China (8,215 deaths in Italy, vis 3,287 deaths in China).

In other words, in just 7 days in Italy, the patients who died of COVID-19 are more than the ones who died in China in 4 months epidemic.

If the two epidemics, Chinese and Italian, had ended on March 26, we could have calculated the CFR (the proportion of cases who eventually die from a

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disease) with the formula: deaths / cases. On March 26, China would have had a CFR value of 4.04% (3,287 total deaths: 81,285 total cases = 4.04); while Italy would have had a CFR of 10.19% (8,215 total deaths: 80,589 total cases = 10.19). In the absence of raw data, we cannot do any verification and we must rely on what the Italian health authorities publish.

g) The partial collapse of the Italian health system

The National Health System (SSN) is very well organized and provides free assistance to all Italian citizens from birth to end of life. There is a national territorial network where children are assisted by a series of pediatricians who can have 800 patients at the most, and can assist them until they reach the age of 16. Adults also have their own general doctors and have a maximum assisted limit of 1,500 people. Then, there is a territorial network of outpatient specialists and a Hospital network that works more efficiently in Central and Northern Italy. In addition, in the 12 night hours there is a territorial medical guard service for all citizens. On March 25, 40 doctors have died because of COVID-19 [16]. 13 general doctors in Lombardy have died (about 20,000 patients have been left without medical assistance), others are in quarantine (thousands more patients are without medical assistance) as the epidemic progresses. On march 25, There are 6,205 health-care workers positive to SARS-CoV-2 test [17]. The main effect produced by the infection of medical personnel is the failure to diagnose COVID-19 disease, which associated with the difficulty and / or impossibility of performing the necessary tests (staff not sufficient compared to the gigantic requests), also due to the coronavirus positivity of the health personnel assigned to perform the tests, leads to death in a non quantified number of subjects without the suspicion of diagnosis, diagnosis and therapy for COVID-19 disease. The WHO guidelines state that patient with mild COVID-19 should only be treated with antipyretics [18]. A case of medium disease may evolve towards spontaneous healing or may aggravate, contract interstitial pneumonia and end up in an intensive care unit, if there is a possibility, otherwise it will die. This losing strategy increases stress on intensive care units, and increases otherwise avoidable mortality to a great extent. This is what happens in Northern Italy. But the primary cause of this collapse is political, because human resources lost over time have not been replaced.

Since the duration of the disease in hospitalized patients is very long (about 2-3 weeks), the possibility of admitting all the people who need it to the existing intensive care units does no longer exists. Hence, many patients who have died of COVID-19 will not enter on official case series. For this reason, the real mortality is much higher than the current one which is already the highest in the world.

h) Italian mistakes

The first news of Italian COVID-19 disease, in Northern Italy, were reported on 21st February 2020. Genomic investigation estimates that SARS-CoV-2 had started to circulate in the Northern Italian territories between mid-December 2019 and 30th January 2020. This research estimates that in Italy there have been different kinds of introductions of SARS-CoV-2, through people who travelled along the peninsula, and people who live in Italy. The phylogenetic investigations have established that one of the first introductions, in the territory of Northern Italy, took place through a traveler from Germany. It can be reasonable to think that it took, at least, one month from the start of SARS-CoV-2 circulation in Italy and the first communication of the case. In this length of time, virus transmission had no containment.

i) Genomic sequencing

Unfortunately, the failure to control genomic sequences by the Istituto Superiore di Sanità (ISS) has led to serious scientific, political and economic consequences since everyone thought that Italy was the source of widespread contagion, while it was only the territory of multiple viral introductions that derived from infected subjects in many parts of the rest of the world and which essentially transited the territory of Northern Italy. This surveillance would also have served other countries to become aware that their citizens were infected and also circulated outside of Italy.

Andersen et al. [19] claim that SARS-CoV-2 is not a laboratory construct, in fact the receptor binding domain (RBD) in the spike protein (S) of SARS-CoV has ~ 96% identity with a coronavirus present in the bat *Rhinolophus affinis*. However, the external subdomain of Spike's RBD of 2019-nCoV shares only 40% amino acid identity with other SARS-related coronaviruses [20].

In any case, the possible intermediate host has not been identified, even if the primitive zoonotic event occurred in the bat. Spike protein binds to the extracellular part of the enzyme ACE2 (angiotensin converting enzyme 2) which is present in many tissues, including the lung and nervous system. In addition, SARSCoV-2 S glycoprotein harbors a furin cleavage site (lacking in the other SARS-like CoVs) at the boundary between the S1 / S2 subunits that sets this virus apart from others SARS-CoV [21]. The S glycoprotein must be cleaved by cell proteases. Proteolytic processing and receptor-binding act in synergy to induce large-scale S conformational changes promoting coronavirus entry [22]. Furin proteases are abundant in the respiratory tract, and in other tissues.

As of 11 March 2020, the sequences of 35 samples connected to the Italian COVID-19 epidemic are available in some databases. Only 2 of these sequences were produced by Italy [23]. The first sequence was produced by the Spallanzani Institute in

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Rome, and belonged to a Chinese woman infected in China; while the second was published by the Istituto Superiore di Sanità, in early March 2020, and derived from a sample obtained from an Italian subject. Before this publication, the genomes of two Brazilian citizens who fell ill on their return and made a trip to Italy had been sequential. The phylogenetic analysis conducted on these two sequences allows Brazilian scientists to hypothesize that there have been multiple virus introductions to Northern Italy [24].

Subsequently, the genome from the first Nigerian patient with COVID-19 who arrived from Italy was sequenced. The phylogenetic tree shows that this genome was introduced in Northern Italy by some persons who came from Germany [25].

Now, we think that the viral genome sequencing, from biological samples obtained from young subjects who fell ill with COVID-19, is necessary.

j) Environmental Stability of SARS-CoV-2

SARS-CoV-2 remains stable on plastic and stainless steel surfaces, while it is less stable on copper and cardboard. The viral titer drops over time [26]. This work confirms that it is necessary to break down the non-human transmission of SARS-CoV-2, as they did in Asia. It is possible that one of the causes of the sustained transmission of the virus in Northern Italy is due to particulate matter. In fact, this territory is home of strong environmental pollution and there is poor air circulation, and in the particulates the viral particles can be adsorbed. If they remain in the particulates, they easily reach the lungs with the breath.

k) COVID-19: an easy diagnosis complicated and delayed by WHO standards

The WHO directives of 29 January 2020 do not allow early detection of COVID-19 disease, because the definition of a suspect case is no longer valid during a pandemic [27]. Since pneumonia due to SARS-CoV-2 infection develops about 8 days after the onset of symptoms, it is difficult to think that a suspect case is subjected to a specific test the first few days of illness, when the transmission of the viral load is maximum. In addition, other cases of illness can occur within 8 days of the contagion of any contacts due to the short incubation period (3-5 days). Furthermore, within these first 8 days of illness this neurotropic virus can enter the central nervous system and produce damage to the bulbar and pontine cardio-respiratory centers.

Rather, attention should also be paid to the loss of the sense of smell and taste, which are symptoms reported by Italian patients in the early stages of the disease.

l) Misinterpretation of the first tests

As of February 26, some countries have published the number of tests and positivity rate for SARS-CoV-2. Our mass media said that we were the best of all in Europe to find out the cases because we did more tests than the others. Table 3 reports these data. However, what we didn't understand, and the French imitated us, that the positivity rates were alarming. In fact, we had 5% positivity rate of the tests and the French had 2.2% positivity rate. Even the USA (3.1% positivity rate) did not understand that this percentage of positivity signaled a widespread circulation of SARS-CoV-2 in those areas subjected to tests.

Table 3: Number of tests and positivity rate for SARS-CoV-2 as of Feb. 26 [28].

Country	Number of tests	Positivity rate
Italy	9,462	5.0%
United States	445	3.1%
France	762	2.2%
Austria	321	0.6%
UK	7,132	0.2%

m) The negative role of Italian scientists on public opinion

Many people were alarmed when the World Health Organization announced in March that COVID-19 has killed 3.4% of the people who have caught it so far a mortality rate far higher than not only the seasonal flu, but also higher than earlier COVID-19 mortality estimates, which were around 2% [29]. Some Italian scientists continue to say in the mass media that seasonal flu is more deadly, even in the presence of over 200 deaths a day [30]. Official data on flu mortality in the 2018-2019 season report 205 deaths [31]. On the single day of 13 March there were 250 deaths from COVID-19 [32]. Then, they say that the virus mainly affects the elderly, while about 60% of infections develop in the age group under 70 years. Even today, some scientists claim that this infection is like a common cold. These facts have heavily affected the civic sense of the population who, by trusting these experts, have exposed themselves to the infection, by not adopting the behaviors useful to avoid it.

In Italy, at June 2020, two new opposite slogans circulate: "The virus has not changed", and "The virus has produced homoplasy".

There are at least two lineages [33] and five different clades [34]. Viruses from both lineages, A and

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B, are still circulating in many countries around the world, reflecting the exportation of viruses from Hubei to other regions of China [33]. A new clade should be at least 2 mutations away from its parent major clade. A clade name consists of the year it emerged and the next available letter in the alphabet [34]. The first two clades are 19A and 19B. These clades were both prevalent in Asia during the first months of the outbreak. The next clade is 20A, that dominated large European outbreak in early 2020. There are another two clades: 20B (Europa), and 20C (North American). Moreover, SARS-CoV-2 genome phylogeny analysis reveals that the D614G mutation appeared to arise from an ancestral D residue. This mutation resides in a highly glycosylated region of the viral spike protein [36]. The mutation spike D614G is of urgent concern [36]. In addition, recombinations require frequent co-infections, that are common with many coronaviruses.

Dudas and Rambaut [37], define the degree of homoplasy of the MERS-CoV virus in these terms: "homoplasy degree to be the number of times a given mutation has originated independently minus one". A homoplasy degree of 1 indicates that a mutation has occurred on two different branches in the phylogeny.

n) Deleterious role of mass media

To all of these negative factors we could add the disastrous communication, which has trivialized the harmfulness of this virus, like the typical phrase: "It is just a silly cold", followed by the phrase: "Death with the virus and not because of the virus", and to finish: "I will stay home". To promote all these slogans many guests, believed to be experts (who were not), had been interviewed on TV shows. In this way, the Italian population moved on from the slogan: "It is just a silly cold" to "The Italian quarantine", and while all of this was happening the damaging: "Death with the virus and not because of the virus" was being promoted. To still trivialize people's death, they proclaimed that only the elderly having previous illnesses dies. It happened to be believed that who died was actually "of a certain age". In other words, the age of death of the elderly from COVID-19 really corresponded to completion of life expectancy of the Italian population. But, we know that the virus is extremely virulent and it also infects young people who are in excellent health, and then find themselves in acute respiratory distress syndrome (ARDS) and have to be admitted to intensive care.

On March 25, the mass media, instead of focusing on the deaths caused by COVID-19, resume a television report from 3 years ago (RAI television) which concerned a scientific article. Aided by a number of Italian scientists, they rushed to show that the SARS-CoV2 virus was not a laboratory construct. The work of *Andersen et al*. [19] had already been clear enough about the laboratory construct hypothesis, but in Italy nothing is ever certain. *Menachery et al*. [38], had just done an experiment using an SARS-CoV infectious clone to generate a chimeric virus that expressing the spike of bat coronavirus SHC014 in a mouse adapted SARS-CoV backbone. These authors had demonstrated that group 2b viruses encoding the SHC014 spike in a wild type backbone can efficiently utilize multiple ACE2 receptor orthologs, replicated efficiently in primary human airway cells, and achieve in vitro titers equivalent to epidemic strains of SARS-CoV. The relevant discovery made by these authors was not understood by the mass media and their experts, but they had told us 4 years in advance that a new SARS-CoV beta can use ACE2 receptors to enter human airway cells.

o) Political mistakes

Each political mistake, is the result of one or more scientific mistakes. Since in Italy there is no totalitarian regime like that of China, political decisions are suggested by scientists who occupy national health institutions, which in turn have been nominated by politicians. Public opinion is then heavily conditioned by groups of scientists who are often not informed about the specific case, but constantly appear on talk shows. They are these groups that invented some slogans that distorted the perception of danger in the population and destroyed the already weak civic sense. Many scientific exponents have close relationships with politics and often condition it directly, and indirectly because of the massive media exposure. So we used opinion leaders to harm us, and we hurt ourselves badly.

The only valid political decision to curb the infection was the military closure of Lombardy and Veneto, starting on February 22nd. But all this has not been done. Furthermore, an environmental remediation has not been completed to bring down the non-human transmission of SARS-CoV-2. In addition, the most serious fact is the "spillover quarantine" which implanted the COVID-19 clusters in Southern Italy, which will soon be the site of a new epidemic.

Dr. Girolamo Giannotta, had done some interviews and participated in two talk shows and had produced some serious alarms that politics and health authorities have ignored. He had warned in advance that the spillover would produce the new COVID-19 clusters in Southern Italy, which has now happened. In addition, he raised the problem of field hospitals that were to be built to house the mass of COVID-19 patients who would later be produced and could not be hospitalized in existing intensive care units [39-41].

p) Immunological enigma

The coronaviruses that live in bats are particularly adapted to evade immune detection and dampen human immune responses. An early and correct innate immune response against the virus is very important; while a late immune response can be very powerful and deleterious (hypersecretion of proinflammatory cytokines, and consequent cytokine

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storm). In addition, the virus easily induces lymphopenia. Therefore, is critical a viral control in an early phase of infection [42]. Unfortunately, CoVs have evolved several mechanisms to inhibit IFN-I induction and signaling [43].

The surface of SARS-CoV-2 is decorated with trimeric spikes that bind to host cell receptors [44]. There is a high identity of receptor-binding domain (RBD) in 2019-nCoV and SARS-CoV, but the difference in the RBD of SARS-CoV and 2019-nCoV has a critical impact for the cross-reactivity of neutralizing antibodies [45]. CR3022, is a neutralizing antibody previously isolated from a convalescent SARS patient that targets a highly conserved epitope, distal from the receptor-binding site, that enables cross-reactive binding between SARS-CoV-2 and SARS-CoV [46]. There is a potential immunosuppressive domain in S1 that could act in the lung and aggravate the disease, and should not be included in future vaccines [47].

V. Conclusion

Active cases grow consistently over time. This long stay in the intensive care unit does not allow all other patients, who fell ill, afterwards, to be hospitalized at the appropriate time, because there are no vacancies in these intensive care units. Poor management of medium cases, in accordance with WHO guidelines, inevitably leads to overload of intensive care units. The progression of clusters in Southern Italy is more pronounced in Campania, Puglia and Sicily. Since the great exodus of people coming from the Northern and going to the Southern Italy occurred on March 7, and a similar exodus, but of smaller proportions occurred on March 14, it is still early to verify if the "measures of social distancing", suggested by the Italian government, have produced effects in terms of slowing the spread of the infection down.

However, at 1 July 2020, increase in total cases and mortality, from COVID-19 in Southern Italy, is presented in table 4. Vice versa, even if the calculation of mortality is incorrect, because the epidemic is not over (+ 109 new cases), the Lombardy has a mortality rate of 17.71% (case / deaths: 94,010 / 16,650), while in Southern Italy it is 9.95%.

Table 4: Increase in total cases and mortality in Southern Italy, from Mar 26 to Jul 1.

Region	Mar 26	Jul 1	Increase in Total cases	Deaths 1Jul	Mortality %
	Total cases	Total cases			
Campania	1,310	4,699	+ 3,389	432	9.19
Puglia	1,182	4,530	+ 3,348	545	12.03
Basilicata	134	402	+ 268	27	6.72
Calabria	393	1,181	+ 788	97	8.21
Sicilia	1,164	3,081	+ 1,917	282	9.15
Total	4,183	13,893	+ 9,710	1,383	9.95

The main cause of the high mortality would be attributable to the partial collapse of the Italian health system, at the moment of maximum pressure, particularly in Lombardy. The partial collapse of the health system is essentially attributable to the contagion of doctors and health personnel who, for this reason, were unable to assist patients as before. As a consequence, many subjects died without a diagnosis, they were not hospitalized and they did not have a diagnostic test while they were still alive. Many health workers have become infected due to a lack of personal protective equipment, in the exercise of their activity, and many of them died.

The best management system was the Korean one. The biggest mistake made by the Italian, French and American governments is to not have understood that the percentage of test positivity was too high and indicative of an imminent health disaster. The British government has deliberately put itself in a losing position, and a 15-day advantage cannot be given to the SARS-CoV-2 virus. It is a failure to rely on the civic sense of the citizens of the western world, since they do not have the same mentality as Japanese citizens, where the recommendations are equivalent to strict recommendations.

As we predicted, the best managemen model was the South Korean one (Tab. 5), and the results are evident on July 1, 2020 [48].

Table 5: Results of the management model of the individual countries.

Countries	Mar 26		Jul 1		Increase in deaths number
	Total cases	Deaths	Total cases	Deaths	
UK	2,129	578	313,483	43,906	+ 43,328
Italy	80,589	8,215	240,760	34,788	+ 26,573
China	81,285	3,287	83,534	4,634	+ 1,349
South Korea	9,241	131	12,850	282	+ 151

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VI. Limitations

Since the data we collect is not in real time, but refers to cases that started 2-3 weeks ago, estimates are affected by these limitations. Furthermore, the raw data are not published in real time by the Istituto Superiore di Sanità (ISS) and we cannot make the best use of them. Because a precise estimate of the case fatality rate is not possible at present, we present in this paper other parameters of COVID-19 Italian epidemic. However, the WHO estimated that the mortality rate is 3.4%, as of march 3.

VII. Future Risk

If this pandemic was generated by a coronavirus that has adapted to only one animal species, not yet identified, pandemic control could occur and re-emergence of the same virus should not occur. Conversely, if another animal reservoir exists, the pandemic may re-emerge in the future. However, if the adaptive process occurred directly in humans, re-emergence would become difficult since the same mutations that favored its diffusion, via the inter-human route, would have to be produced.

The other major risk is ecological because this large circulation of SARS-CoV-2, which occurs in early spring in Europe, coincides with the exit from the hibernation of bats, and in the Veneto [49], and Sardinia [50] there are bats that host several coronaviruses. If SARS-CoV-2 infects bats, recombinant events are possible with the risk of emergence of a new pandemic. Furthermore, the wide circulation of SARS-CoV-2 in the world, allows the virus to produce new mutations that have already led to the second clade G, and which could lead to new more or less invasive clades, compared to the two currently known.

VIII. Perspectives

a) Virology labs

Recombinant coronaviruses, generated by reverse genetic systems have been used to produce chimeric coronaviruses that could be useful as coronavirus vaccines, and for the analysis of the pathogenesis of coronavirus [51]. This means that scientists have been manipulating these viruses in the laboratory for several years, and a biological incident can never be excluded. Laboratories handling coronaviruses may find themselves facing microbes that need a higher level of biosecurity than their current standard. For example, level 3 labs should not manipulate coronaviruses that need level 4 security measures. Hazard Group 4 of viral pathogens are organisms that causes severe human disease and is a serious hazard to laboratory workers. It may present a high risk of spread to the community and there is usually no effective prophylaxis or treatment [52]. Wuhan lab was certified as meeting the standards and criteria of BSL-4 by the China National Accreditation Service for Conformity Assessment (CNAS). Many staff from the Wuhan lab have been training at a BSL-4 lab in Lyon. The Wuhan lab focus on the control of emerging diseases, store purified viruses and act as a World Health Organization 'reference laboratory' linked to similar labs around the world, but SARS virus has escaped from high-level containment facilities in Beijing multiple times [53]. Moreover, Moloney Murine Leukemia Virus (M-MLV), contaminates reverse transcriptase (RT) reagents and also have been detected in previous virome analysis of insectivorous bats in China [54].

The biosecurity level of virology labs must take into account that viruses with all types of genomic structures and replication strategies, have been discovered in bats, and coronaviruses appear to have evolved a fine-tuned balance between masking of the RBM, to limit neutralization by the humoral host immune response, and their necessary exposure, to enable receptor recognition and infection of host cells [55]. Moreover, viral gene fragments identical or quite similar to those of MERS-CoV have also been recovered in bats, raising again the possibility that the bat acts as the natural reservoir of MERS-CoV [56-58]. Given that MERS viral gene fragments are in bats, gene recombination may have allowed the furin cleavage site to be transferred from the MERS-CoV to the new SARS-CoV-2. But this event can take place in a bat that lives in a cave, as in a bat housed in the virology laboratory. All this to reinforce the alarm on virology research laboratories that, perhaps, do not have the biosecurity standards adequate to the firepower expressed by the new coronaviruses.

In summary, the virus derives from bats that live in Yunnah Province, the epidemic broke out in Wuhan (Hubei Province) at 1,186 km away, an intermediate host was not identified after the initial zoonotic event, it is not a laboratory construct but the product of a gene recombination that can take place in a Yunnah cave or in a Wuhan virology laboratory, has a furin cleavage site such as MERS-CoV, is subject to manipulation in virology laboratories, and for this it needs of high biosecurity standards that, perhaps, not all the laboratories that handle them have.

b) Vaccines

When comparing natural disease with vaccination practice it is necessary to remember that the number of antigens presented to the immune system, during viral infection, is significantly higher than the number of antigens that may be present with a candidate vaccine. This allows a wider production of different antibodies directed against different viral

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epitopes. In addition, binding and neutralizing antibodies can be produced, but only neutralizing antibodies can stop the virus. With SARS-CoV-2 vaccines, researchers' main safety concern is to avoid a phenomenon called antibody-dependent enhancement (ADE), in which vaccinated people who do get infected develop a more severe form of the disease than people who have never been vaccinated [59]. ADE is a mechanism through which dengue viruses, feline coronaviruses, and HIV viruses take advantage of anti-viral humoral immune responses to infect host target cells. Antibodies against SARS-CoV spike proteins may trigger ADE effects [60]. Immunized ferrets, with recombinant modified vaccinia virus Ankara (rMVA) expressing the SARS-CoV spike S protein, exhibited strong inflammatory responses in liver tissue. Vaccination with rMVA expressing SARS-CoV S protein is associated with enhanced hepatitis [61]. Vaccine-induced antibodies that enhance entry of virus could increase the frequency of B cell infection in vaccinated subjects and alter disease on subsequent exposure to SARS-CoV [62]. Moreover, injection of SARS-CoV vaccines in mice led to the occurrence of Th2-type immunopathology, suggesting that hypersensitivity to SARS-CoV components was induced [63]. Most vaccines carry with them the possibility of side effects that must be considered in ultimately deploying them to the human population [59].

There are more than 100 candidate COVID-19 vaccines in development [64]. The Moderna vaccine consists of an RNA molecule, and it is designed to train the immune system to make antibodies that recognize and block the spike protein [59]. This study has no history of change, and placebo is truly placebo (saline). The press release from Moderna is not very clear [65]. However, all 45 participants were seroconverted, and only 8 out of 45 patients had data on neutralizing antibodies. Since binding and neutralizing antibodies can be produced, we will have to know what is the percentage of subjects that produce neutralizing antibodies.

ChAdOx1 nCoV-19 is an other vaccine currently being investigated (ClinicalTrials.gov NCT04324606). The ChAdOx1 viral vector was developed at the University of Oxford, and consists of an attenuated adenovirus capable of producing the spike protein of SARS-CoV-2. The study starts with a serious scientific mistake, because the menigococcal vaccine (MenACWY) is indicated as placebo [66], while the real placebo does not contain any biologically active substance. In just two months, this study has a history of 8 changes. Conversely, the study started in South Africa [67] uses 0.9% saline as a true placebo (ClinicalTrials.gov NCT04444674).

c) Monoclonal antibodies and convalescent plasma

Most monoclonal antibodies against SARS-CoV spike proteins promoted SARS-CoV infection [60]. The vast majority of patients who recover from COVID-19 illness develop some level of circulating neutralizing antibodies to various SARS-CoV-2 proteins, 2-3 weeks following infection. Convalescent plasma transfusion appears safe [68], but the risks of plasma transfusion include: allergic reactions, transfusion-associated circulatory overload, transfusion-associated acute lung injury, and ADE to the next infection (that has not been documented to date).

Ethical Approval and Consent to participate.

Not applicable.

Our work does not use data concerning patients we follow, but the data are public and derive from the Italian Civil Protection.

Consent for publication

Not applicable

Availability of supporting data

We have transcribed the Civil Protection data on Exel sheets that we can make available for the journal.

Competing interests

We have no conflicts of interest.

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Authors' contributions

Dr Girolamo Giannotta is responsible for writing the text.

Nicola Giannotta took care of the bibliographic research, and produced the part concerning the genomic sequencing.

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